



UNTANGLING THE WEB OF

ANTIRETROVIRAL PRICE REDUCTIONS

16th Edition – July 2013

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THE MSF ACCESS CAMPAIGN

In 1999, on the heels of MSF being awarded the Nobel Peace Prize—and largely in response to the inequalities surrounding access to HIV/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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MSF AND HIV

Médecins Sans Frontières (MSF) began providing antiretroviral therapy to a small number of people living with HIV/AIDS in 2000 in projects in Thailand, South Africa and Cameroon. At the time, treatment for one person for one year cost more than \$10,000. With increased availability of low-cost quality antiretroviral drugs (ARVs), MSF currently provides treatment to 285,000 people, implementing treatment strategies to reach more people, earlier in their disease progression, while increasingly encouraging patients to take on a more central role in the management of their care.

Over the past 13 years, the MSF Access Campaign has been monitoring the patent barriers, prices and availability of ARVs through *Untangling the Web* and pushing for the uptake of policies that promote access to affordable quality medicines. Due primarily to generic competition, the price of ARVs has dropped by more than 99% over the last decade, but the price of the newest drugs, already needed by some people in MSF projects, is prohibitive and a source of great concern both for MSF and for national treatment programmes.

LATEST RESOURCES FROM MSF ON HIV

PATENT OPPOSITION DATABASE

The Patent Opposition Database was launched by the MSF Access Campaign in October 2012 as an online space where civil society can share the resources and tools needed to oppose patents on medicines. The Database gathers contributions from around the world. It allows documents to be shared, arguments to be replicated and new alliances to be forged with the aim of successfully opposing patents and ultimately improving access to medicine in developing countries. To find out more about patents which block access to essential medicines and what you can do to challenge them, or to contribute by sharing resources, visit:

 www.patentoppositions.org

PUTTING HIV TREATMENT TO THE TEST: A PRODUCT GUIDE FOR VIRAL LOAD AND POINT-OF-CARE CD4 DIAGNOSTIC TOOLS

Including technical and pricing information for 14 commercialised or pipeline diagnostic tools, this report is a guide for policymakers, treatment providers and advocates interested in learning more about the use of laboratory-based and point-of-care viral load and CD4 diagnostics for treatment initiation and monitoring in resource-poor settings.

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ACCESS TO AFFORDABLE ANTIRETROVIRALS IN 2013

NEW GUIDELINES AND NEW NEEDS, NEW PROGRESS AND NEW THREATS

There are now more than nine million people in developing countries receiving antiretroviral therapy (ART), including more than seven million in Africa.^{1,2}

There has been new momentum at the highest political levels to put plans into place that will make the most use of the recent science showing ART itself both saves lives and stops HIV from spreading. International funding, however, remains largely stagnant across the board and will need to be increased to achieve the goals of saving more lives through treatment, while dramatically reducing HIV transmission.

In its 2013 consolidated HIV treatment guidelines, the World Health Organization (WHO) is recommending a number of changes that will improve treatment in developing countries, first and foremost earlier initiation of treatment at a threshold of CD4 cell count of 500 or below. The new guidelines also recommend ART for life for all pregnant women with HIV ('Option B+') in countries with generalised epidemics, and as an option for all countries, as well as immediate treatment for HIV-positive individuals with HIV-negative partners ('sero-discordant' couples).

These recommendations increase considerably the number of people on treatment, with WHO estimating in 2012 that around 25 million people could be in need.³ WHO also recommends routine viral load monitoring in order to detect and correct adherence problems as they arise, or switch people to alternative treatment if

necessary. Further, tenofovir (TDF) is the clear preferred first-line regimen for adults, while treatment recommendations for children are simplified and strengthened, with ART recommended for all HIV-positive children under five years of age, and a boosted protease inhibitor recommended for all children under three.

Because millions of people need to be initiated and sustained on treatment regimens for life, it is as critical as ever to ensure ARVs are affordable.

Competition among generic producers was instrumental in bringing down the price of the first generation of ARVs, and is one of the key reasons treatment could be scaled up to millions of people. Today, first-line ART is available for just under US\$100 per person per year (ppy), which is a 99% decrease from 2000, when treatments still under patent were priced at more than \$10,000 ppy.

But the situation today is different and the progress achieved is once again under threat. Key countries, especially India, where generics are produced, now grant medicine patents in order to comply with their international obligations as members of the World Trade Organization (WTO). Newer ARVs are already patented in these countries, meaning that production of affordable generic

medicines is now restricted, keeping monopoly prices high.

With upwards of 55 million people expected to need ARV therapy by the year 2030,⁴ global patent rules are contributing to a looming crisis as current drugs lose their effectiveness and their newer, patented replacements are priced out of reach for all but the wealthy.

While the prices quoted by manufacturers for first- and second-line regimens continue to fall—largely thanks to the impact of generic competition with new suppliers entering the market—the prices of the newest drugs continue to be astronomically high, primarily because of patents in producing countries such as India that block generic competition. And while the Indian Supreme Court's decision to reject Swiss pharmaceutical company Novartis's attack on India's patent law will safeguard first- and second-line ARVs currently in generic production, additional threats to access to medicines loom large in the form of patents covering new compounds, restrictive provisions in free trade agreements which include additional intellectual property obligations that block generic competition, and voluntary licence agreements between originator and generic drug producers that exclude many countries where people with HIV live.

PRICES OFFERED, PRICES PAID

FIRST-LINE TREATMENT: AT LAST, MORE PRODUCERS OF THE ONE-PILL-PER-DAY OPTION

The price of first-line ARVs continues to fall as more manufacturers enter the market, fostering price-busting competition. The one-pill-a-day fixed-dose combination of tenofovir/lamivudine or emtricitabine/efavirenz (TDF/3TC or FTC/EFV) is recommended by WHO as the preferred first-line treatment option.

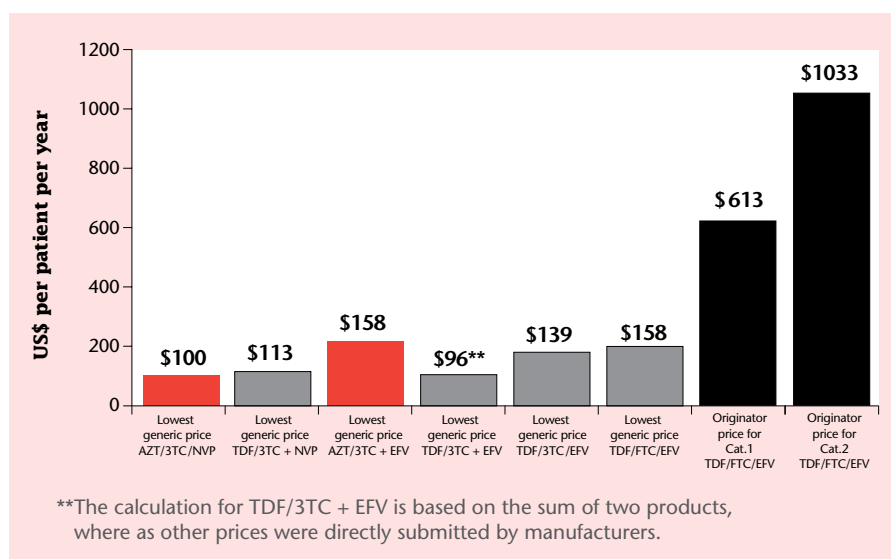
The one-pill-a-day TDF/3TC/EFV combination has seen a price decrease of 19% compared to last year, from \$172 to \$139 ppy for the most affordable quality-assured option – see Graphs 1 and 2. The entry of one additional quality-assured producer, Hetero, has broken the stronghold that producer Mylan had on the market, and with the expected entry of two further manufacturers that are currently seeking approval for this product from the WHO prequalification programme or the US Food and Drug Administration, the price will likely fall further.

The South African government, in a November 2012 tender, negotiated the lowest global prices for the TDF/3TC/EFV combination, ranging from \$114 ppy to \$121 ppy, but these prices are not yet available beyond South Africa.⁵ More affordable quality-assured generic options are available, but they are not one-pill-a-day options. TDF/3TC + EFV, a first-line regimen split into two pills taken once daily, costs \$96 ppy.

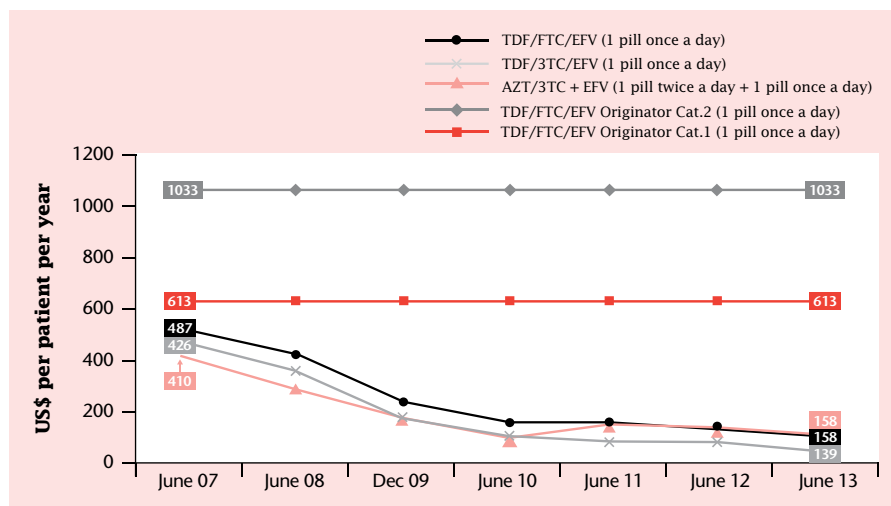
Generic options of the one-pill-a-day combination, which have fallen by 67% since 2007, are considerably cheaper than the originator company versions, which have remained constant since 2007 at \$613 for low-income countries, and \$1,033 for lower middle-income countries (for the therapeutically equivalent TDF/FTC/EFV).

TDF is better-tolerated than zidovudine (AZT) and can be taken once daily, which helps people adhere to their treatment and therefore stay on their first regimen longer. A simplified regimen

GRAPH 1: THE PRICE OF DIFFERENT FIRST-LINE REGIMENS TODAY



GRAPH 2: THE EVOLUTION IN PRICE OF DIFFERENT FIRST-LINE REGIMENS



also facilitates treatment scale-up. In addition, first-line regimens based on AZT, rather than TDF, which WHO only recommends as an alternative to TDF, are slightly more expensive, and require twice-daily dosing. The most affordable

version of AZT/3TC/NVP (one pill taken twice daily) is \$100 ppy, and the AZT/3TC + EFV regimen (one pill once daily plus one twice) is \$158 ppy, representing a 16% and 24% price decrease over last year.

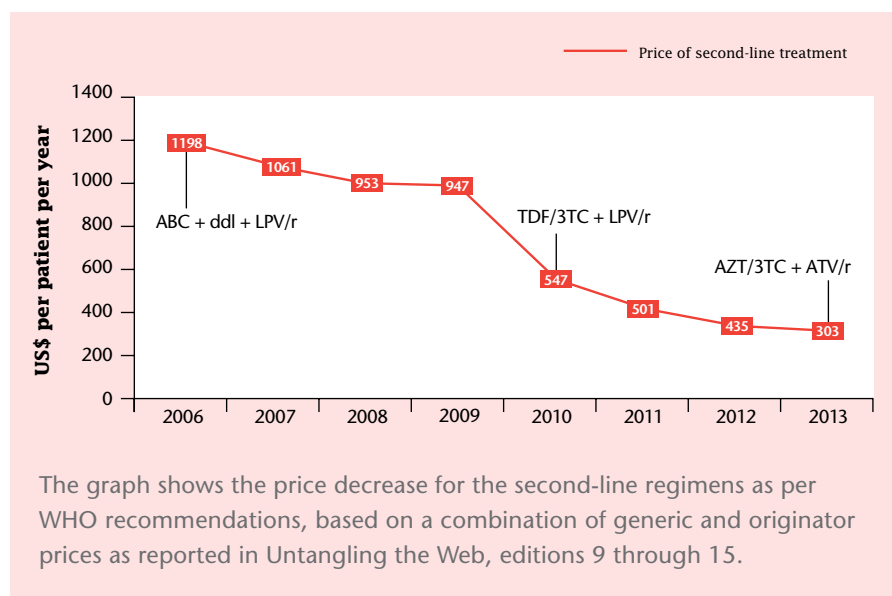
SECOND-LINE TREATMENT: COMPETITION IS DRIVING PRICES DOWN

With growing numbers of people on treatment—and viral load monitoring slowly becoming available to help detect people who need to switch treatment—the need for second-line therapy is increasing. WHO recommends both lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r) as protease inhibitors for second-line therapy, with ATV/r having the advantage of once-daily dosing.

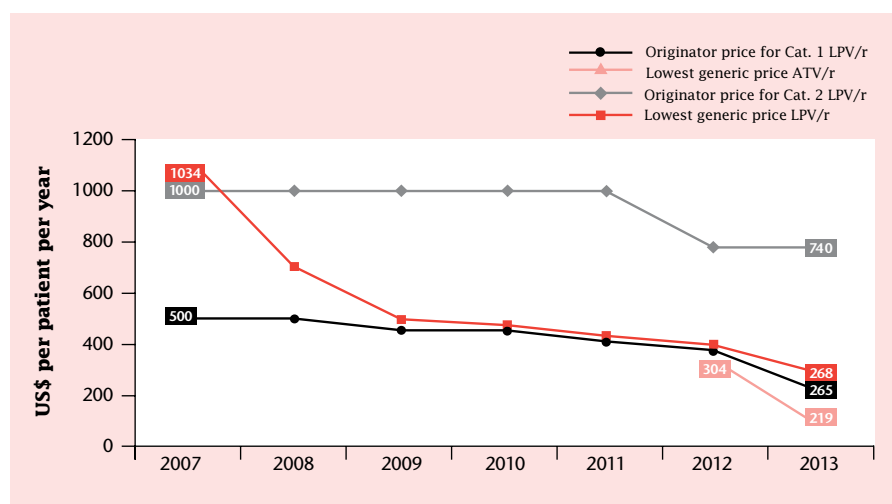
Although it remains more than twice the price of first-line treatment, the price of WHO-recommended second-line treatment has fallen thanks to generic competition by a substantial 75% since 2006, from \$1,198 to \$303 ppy for today's most affordable second-line combination – see Graph 3. The second-line price decrease occurred largely because patents were successfully opposed in India on LPV/r, allowing for generic competition to bring prices down over several years. There are now four quality-assured generic producers of LPV/r.

A further downward trend in second-line pricing has come as a result of the fixed-dose combination of ATV/r becoming available, after a patent opposition on ritonavir (RTV) in India enabled generic production of RTV, which could then be used to boost protease inhibitors other than lopinavir. This has loosened the dominance of LPV/r in the market – see Graph 4. ATV/r has seen a 28% price decrease since last year, from \$304 to \$219 ppy, and there was also a 28% decrease in the price of LPV/r (\$368 to \$265 ppy), with the AbbVie (Abbott) product continuing to be marginally less expensive than the generic. However, middle-income countries falling into Abbott's 'category 2' (see Annex 2) continue to pay a significantly higher price – 64% more at \$740 ppy.

GRAPH 3: MOST AFFORDABLE SECOND-LINE TREATMENT OPTION AS PER WHO GUIDELINES



GRAPH 4: THE EVOLUTION IN PRICE OF BOOSTED PROTEASE INHIBITORS FOR SECOND-LINE REGIMENS



STOP PRESS:

At the time of going to press, the first generic raltegravir product became available for procurement based on quality assessment performed by the Expert Review Panel of Global Fund. The manufacturer, Hetero, was contacted but did not submit prices in time for inclusion in this report.

VIRAL LOAD TESTING IN RESOURCE-LIMITED SETTINGS

In its new 2013 ARV treatment guidelines, the WHO strongly recommends viral load monitoring at six and 12 months after treatment initiation and then at least every 12 months thereafter. While viral load testing is the gold standard for treatment monitoring in developed countries, it remains scarce in developing countries.

Routine viral load testing is critical for two reasons. Firstly, it can prevent unnecessary switching of people to more expensive second-line regimens (which occurs when using clinical or immunologic – CD4 cell count – monitoring) by detecting adherence problems early on, before resistance has developed.

These problems can then be addressed through intense and targeted adherence counselling. Secondly, it can detect those people who are failing their treatment and indeed need to be switched to another regimen early enough to keep them healthy, as opposed to CD4 testing, which detects treatment failure far later – maybe too late.

However, because of cost and complexity, viral load monitoring has only been available in very few places in resource-limited settings. Of 23 developing countries surveyed by MSF in 2012, only four had access to viral load testing in accordance with their national treatment guidelines.⁶

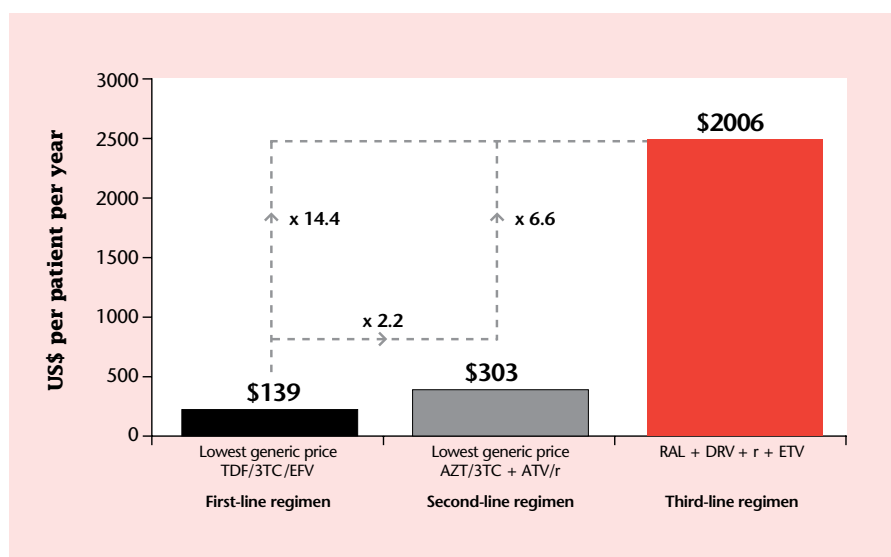
With support from UNITAID, MSF will be implementing a three-year project to evaluate various viral load and CD4 testing technologies in eight projects across seven countries. The project will aim to establish the feasibility of routine viral load testing in resource-limited settings, assess which existing and pipeline devices are best fit to resource-limited settings and have the greatest impact on treatment outcomes, and determine to which extent viral load testing can be decentralised. For more information on the products available and their prices, see MSF's new report *Putting HIV Treatment to the Test: A Product Guide for Viral Load and Point-of-Care CD4 Diagnostic Tools*.

SALVAGE THERAPY WITH THE NEWEST DRUGS: PRICES REMAIN SKY-HIGH IN ABSENCE OF COMPETITION

New medicines and new regimens are needed as resistance increases and spreads: the prevalence of baseline drug resistance to any ARV eight years after roll out is on average 7.4%, and is increasing in southern Africa by 14% per year.^{7,8} Additionally, some newer or pipeline medicines may also offer additional benefits of being more effective or better tolerated and thus have the potential to become preferred regimens in the future.

There are currently no WHO-prequalified generic versions of the three new drugs raltegravir (RAL), etravirine (ETV) or darunavir (DRV), which are used for third-line or salvage therapy, and their prices remain extremely high. The best-possible price for a potential third-line regimen containing RAL, DRV/r and ETV is \$2,006 in the poorest countries, which is almost 15 times more expensive than the one-pill-a-day first-line treatment, and more than six times

GRAPH 5: PRICE COMPARISONS OF FIRST-LINE, SECOND-LINE AND POSSIBLE THIRD-LINE TREATMENT REGIMENS



as expensive as the most affordable second-line regimen – see Graph 5.

Although this represents a 19% decrease from last year, such high

prices are extremely problematic as more and more treatment programmes need access to these drugs for people who have exhausted all other treatment options.

Product	Country	Price per patient per year (US\$)
Raltegravir 400mg tablet	Armenia	13,213
	Georgia	13,225
	Paraguay	7,008
Etravirine 100mg tablet	Jamaica	6,570
	Paraguay	7,782
	Ukraine	6,679
Darunavir 600mg tablet	Armenia	8,468
	Jamaica	6,570
	Morocco	5,356
	Thailand	4,760

TABLE 1: ASTRONOMICAL PRICES PAID FOR THIRD-LINE REGIMENS

This table shows the prices paid by certain middle-income countries for some of the newest ARVs in 2012, based on the Global Fund’s Price and Quality Reporting database. Most originator companies have discontinued offering standardised price discounts in middle-income countries, and replaced this with case-by-case price negotiations, which lead to astronomically high prices paid.

Some countries are paying astronomical prices for these drugs: in 2012, Georgia paid \$13,225 for one person’s one year supply of RAL, while Paraguay paid \$7,782 ppy for ETV, and Armenia and Thailand paid \$8,468 ppy and \$4,760 ppy, respectively, for DRV – **see Table 1.**

These high prices are in large part a reflection of the fact that companies in the last few years have replaced standardised discount programmes in countries classified as ‘middle-income’ with a model of case-by-case price negotiations. This system lacks transparency and leads to countries paying exorbitantly high prices.

With the WTO’s TRIPS agreement being implemented in key manufacturing countries and several of the newest HIV drugs patented in countries such as India, the sort of automatic generic competition that brought prices down so dramatically for older generations of ARVs will not be possible for these newer medicines. More than 80% of the ARVs used in developing countries are produced in India.⁹

The only prospect for access to lower prices for these drugs is for governments – particularly India, but also countries seeking to import

affordable generics, and where patent barriers prevent this – to use patent law safeguards, for example by issuing compulsory licences that could allow generic manufacturers to produce and market affordable versions of patented medicines. Alternatively, the companies themselves could lower the prices either directly or through voluntary licence agreements with other manufacturers. However, as long as these agreements continue to exclude ‘middle-income’ countries, persistently high prices shut down hopes for access (**see Annex 3** for details on voluntary licences).



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LOOKING TO THE PIPELINE: PROMISING ARV CANDIDATES

Looking into the ARV drug development pipeline, two candidates stand out that appear to have important attributes for use in developing countries:

Tenofovir alafenamide (TAF):

TAF is a pro-drug or precursor drug to tenofovir (TDF). While TDF currently forms the backbone of preferred first-line regimens in adults, and is effective, safe and well tolerated, side effects can be an issue for certain patients (such as people with pre-existing risk factors for kidney problems). TAF has so far been shown to be extremely effective, with fewer side effects than TDF. This is because TAF concentrates well inside cells but does not have very high levels in the plasma. This also means that each pill can contain less of the active ingredient and be just as effective, which is potentially price-lowering. TAF is being co-formulated with emtricitabine, elvitegravir and cobicistat and is currently in Phase III trials being conducted by Gilead.

Patents for TAF have been filed and granted in many countries, including India, which will not expire before 2021. Given the importance of this drug, a wide array of access strategies should be developed and followed in different countries. The main patent is potentially weak and can be opposed in countries where patent opposition systems are functional. In India, enabling generic production of TAF will first require a strategy to revoke the the strategy to revoke the patent.¹⁰ Other access strategies including broad licensing through the Medicines Patent Pool could also be explored.

Dolutegravir (DTG): DTG is a new integrase inhibitor with significant benefits over current drugs in this class. It is extremely potent, can be dosed once daily and unlike earlier integrase inhibitors, has a high barrier to resistance. DTG is being co-formulated by ViiV into a single tablet regimen of ABC/3TC/DTG, which has shown to be potentially more

effective than TDF/FTC/EFV, the currently preferred first-line single-tablet regimen. DTG was submitted by ViiV for US FDA approval in February 2013 and will receive a fast-tracked 'priority review.'

Patents for DTG have been granted or are pending in several countries, and the basic patent will not expire before 2016. In India, a patent opposition was filed, while the patent application is pending. Although the Medicines Patent Pool and ViiV recently concluded a Memorandum of Understanding under which the company commits to licence its pipeline products for paediatric use in 118 countries once approved by drug regulatory authorities, there is no known voluntary licence yet concluded for the adult formulation of DTG. ViiV's existing voluntary licences for adult formulations are quite restrictive and only include least-developed countries.



POLICIES TO BRING PRICES DOWN

The past year has seen a number of critically important advances for access to medicines, including Novartis's loss of its seven-year legal battle against the Indian government, and further moves by developing countries to override patents in the interest of public health. At the same time, threats persist in the form of ongoing free trade agreement negotiations that could choke off the production and distribution of affordable generic medicines in developing countries, as well as in voluntary licence negotiations that continue to exclude a number of countries.

ADVANCES:

NOVARTIS'S ATTACK ON THE INDIAN PATENTS ACT AND ITS STRICT PATENTABILITY CRITERIA FAILS:

In April 2013, India's Supreme Court issued a landmark ruling against Swiss pharmaceutical company Novartis's seven-year attack on India's patent law. In 2005, India adopted a strict medicines patent law that, while ensuring patent protection for new pharmaceutical compounds, makes it tougher to get a patent on new forms of existing medicines. The law was designed with the objective of stopping 'evergreening,' a common abusive patenting practice in the pharmaceutical industry aimed at filing and then obtaining separate patents relating to different aspects of the same medicine. India's tougher patentability standard – enshrined in Section 3d of the

country's patent law – was at the crux of Swiss company Novartis' attack.

Since 2005, this part of India's law has been instrumental in protecting generic production of first- and second-line HIV medicines in India used to treat people in MSF projects and across the developing world. Patent applications on improved versions of adapted formulations for babies and children, fixed-dose combinations that simplify treatment by combining multiple medicines into one pill, and formulations that are better able to tolerate the heat – all of which are vital for people in developing countries – were systematically rejected by the

Indian patent offices, largely following 'patent oppositions' filed by civil society or generic manufacturers to prevent unwarranted patenting.


Following the rejection of its patent application for a cancer drug, based on this part of India's law, Novartis sought to change the law through the courts. With India's Supreme Court now having ruled against Novartis, the Indian government will continue to be able to protect public health against abusive patenting practices and unwarranted monopolies and keep the door open as much as possible for access to affordable medicines for millions of people in developing countries who rely on quality generics made in India.

COUNTRIES EXERCISE THEIR RIGHT TO ALLOW LOW-COST GENERIC VERSIONS OF PATENTED DRUGS IN THE INTEREST OF PUBLIC HEALTH:


The intellectual property rules agreed at the WTO also lay down what countries can do when patented life-saving medicines are priced out of reach. By issuing a 'compulsory licence' (CL), governments can allow manufacturers other than the patent-holder to produce generic versions of patented medicines. Thailand and Brazil issued such CLs in 2006 and 2007 for a number of ARVs, bringing the price of these medicines down significantly for their national treatment programmes.


However, countries issuing CLs can face significant commercial and political retaliation. For example, in 2007, pharmaceutical company Abbott retaliated against Thailand's issuance of a CL by refusing to complete registration of seven other medicines in the country.¹¹

Nevertheless, there are now signs that CLs are being used more frequently to increase access to life-saving medicines, demonstrating an important political commitment to implement flexibilities outlined in the WTO TRIPS Agreement:

-  In March 2013, the Indian Intellectual Property Appellate Board upheld a March 2012 decision by the patent controller to issue a CL for a patented cancer drug produced by Bayer – the first time the Indian government has applied this measure. In addition, the government has since expressed an interest in issuing public notifications that identify unaffordable drugs (for the Indian market) and inviting generic production under a CL.¹² If compulsory licensing becomes routine, licences could be issued

for several new HIV drugs that are patented in India and priced out of reach. A new approach to CLs in India would have a major impact on the price of new ARVs across the developing world.

-  In September 2012, the Indonesian government issued a compulsory licence (a 'government use' decree) for seven drugs that treat HIV and hepatitis B that it deemed unaffordable for the national treatment programme.

-  In November 2012, Ecuador issued a compulsory licence on abacavir and lamivudine. This follows a similar CL issued by the government in 2009 for lopinavir/ritonavir.



MEDICINES PATENT POOL SIGNS NEW LICENCE WITH PHARMACEUTICAL COMPANY, COVERING MORE COUNTRIES:

In February 2013, the Medicines Patent Pool signed its second licence with a pharmaceutical company, this time with ViiV (the joint venture between Pfizer and GlaxoSmithKline) covering a paediatric formulation of ABC.

The licence has an improved geographical scope over the Patent Pool's 2011 licence with Gilead. However, the licence still excludes several middle-income countries,

including China, Brazil, Mexico, Russia, Kazakhstan, Kyrgyzstan and Ukraine. In Ukraine, GSK has enforced its patents against generic companies, preventing domestic use of generic versions of ABC.

MSF has urged ViiV to include patents on both adult and paediatric versions of its promising new integrase inhibitor dolutegravir in the Patent Pool with a broad geographic scope that ensures people in need are covered.

Patents on other medically important drugs such as LPV/r continue to create barriers to treatment in some developing countries. AbbVie (formerly Abbott) has yet to start negotiations with the Medicines Patent Pool to license its HIV products. A voluntary licence through the MPP on LPV/r could help to facilitate development of necessary fixed-dose combinations, including paediatric versions, and contribute to additional price reductions.

BRAZIL REAFFIRMS HEALTH AGENCY'S RIGHT TO EXAMINE PATENTS AND PROPOSES AMENDMENTS TO PATENT LAW:

In April 2013, the Brazilian government announced that the National Health Surveillance Agency (ANVISA) would continue to have the right to examine patent applications for pharmaceuticals, prior to examination by the patent office. A review by ANVISA before patent applications are examined by the National Institute of Industrial Property is an important step to prevent evergreening. Brazil's decision to maintain and better define the role of ANVISA in the analysis of

pharmaceutical patents can help ensure that affordable medicines are available where a patent fails to meet the country's patentability requirements.

Building upon this momentum, legislation was tabled in April 2013 to reform Brazil's 1996 Industrial Property Act. The legislation, if enacted in its current form, could improve the government's management of intellectual property in order to benefit public health. Key amendments in the

legislation include: limiting the patent term to a maximum length of 20 years, strict patentability requirements and improvements to the existing pre-grant opposition mechanism, ensuring that data exclusivity regimes are prohibited, and introducing a non-commercial public use mechanism (compulsory licensing). Finally, the legislation would codify the recent announcement of the government that confirms ANVISA's role to examine patent applications for pharmaceuticals.

THREATS:

FREE TRADE AGREEMENTS COULD CHOK OFF GENERIC PRODUCTION:

❖ **The EU-India Free Trade Agreement (FTA)** negotiations, now in their sixth year, continue to include measures that could seriously restrict production of generic medicines in India, despite several of these measures having been rejected at the EU level in the Anti-Counterfeiting Trade Agreement (ACTA) negotiations in 2012. While certain harmful provisions such as data exclusivity and patent term extensions have been removed from the negotiations as a result of civil society pressure, intellectual property (IP) enforcement measures could lead to increased seizures of legitimately-produced generic medicines being exported from India to other countries, much like the seizures that took place at several European ports and airports between 2008 and 2010. Furthermore, enforcement provisions could draw treatment providers such as MSF into legal proceedings, simply for using generic medicines.

In addition, *investment* provisions could allow multinational companies to sue the Indian government for taking measures in the interest of public health (such as issuing a compulsory licence or the patent office rejecting a patent), if the company deems this action to ‘expropriate its IP’ and interfere with its ‘investment’ in the country. Such legal proceedings, enabled by investment provisions in other FTAs, have already been initiated by the multinational pharmaceutical industry in Canada. In 2012, US pharmaceutical company Eli Lilly started proceedings against the government of Canada through the North American Free Trade Agreement’s (NAFTA) investor-to-state dispute mechanism, claiming that the decisions of a Canadian court to invalidate its patent on the medicine atomoxetine violated Canada’s obligations under NAFTA and the WTO. Eli Lilly is seeking \$100 million in compensation.¹³

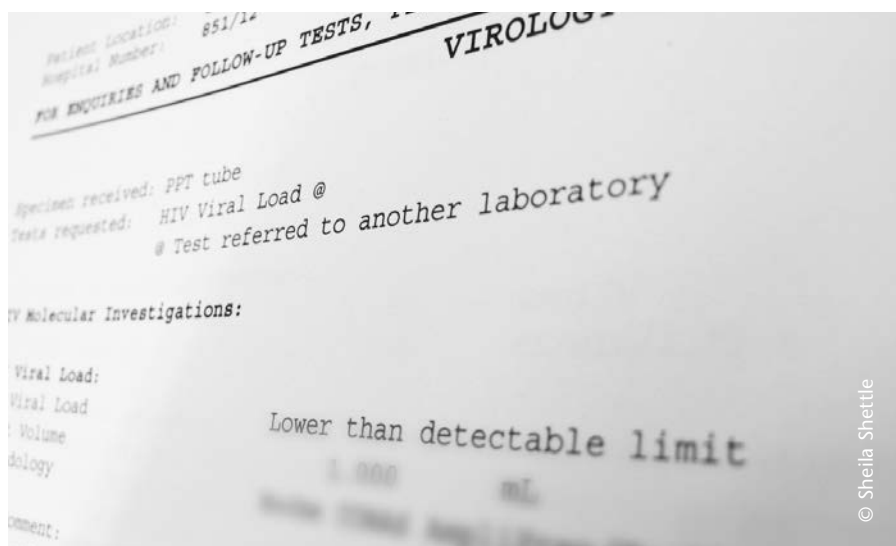
It is crucial that the Indian government continue to resist provisions that will harm access to medicines as the negotiations enter their final stage. The Indian Parliament has already signalled its intention to carefully monitor the agreement for its potential impact. In April 2013, the chairman of the Parliamentary Standing Committee on Commerce wrote a letter to the Indian Prime Minister calling on him to defer the signing of the EU-India FTA until the Committee fully debates the issues, including access to medicines concerns, that have been raised by States, NGOs and other stakeholders.¹⁴

❖ **Negotiations for an FTA between the European Union and Thailand** were launched in March 2013. Thai civil society groups are gravely concerned about the potentially negative impacts the FTA could have on access to affordable medicines.

This proposed FTA includes several intellectual property provisions that exceed the requirements in the WTO TRIPS agreement (‘TRIPS plus’ measures), including patent term extensions, data exclusivity and border measures, as well as foreign investment protection, including secretive arbitration mechanisms for the settlement of disputes between the state and the private sector. The governments have set an ambitious timeframe to complete negotiations, with the FTA

scheduled for approval before the Thai Parliament in 2014 negotiations, with the FTA scheduled for approval before the Thai Parliament in 2014, a year before Thailand’s preferential trade benefit agreement with the EU expires.¹⁵ This raises concerns that the Thai government will accept strict IP provisions for medicines in order to meet this deadline.

❖ **The Trans-Pacific Partnership Agreement (TPP)**, under negotiation between the United States and more than ten Pacific-rim countries, poses another significant threat to access to medicines. The proposed agreement would set a new high standard for IP across Asia and the Americas that would dramatically expand monopoly protection for medicines. In the negotiations, the US is pushing harmful measures such as data exclusivity, patent-term extensions, new forms of IP enforcement, expansion of the scope of patentability, and the outlawing of pre-grant oppositions. The US has indicated that it eventually wants standards promulgated under the TPP to be adopted by countries across Asia and Latin America, which could include countries that produce affordable generic medicines or have sizeable populations of people living with HIV. Additionally, the TPP could serve as the precedent for future trade agreements pursued by the US, which could also involve such countries.





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VOLUNTARY LICENCES CONTINUE TO BE NON-TRANSPARENT AND EXCLUDE MIDDLE-INCOME COUNTRIES:

Voluntary licences (VLs) continue to dominate as the preferred business model of originator companies to sell new HIV medicines in low-income countries. Annex 3 covers VLs signed between originator and generic companies on ARVs. VLs raise serious concerns – almost all licences exclude middle-income countries. In addition, the lack of transparency is a problem, and since substantive information about contractual terms and licensing details are not disclosed with such licences, it is difficult to comment upon and evaluate their actual impact. A few companies provide information about the geographic scope of the agreements and the nature of licensing arrangements, but otherwise omit the crucial details.

The Medicines Patent Pool, which has a public health mandate, has approached voluntary licensing with transparency as a key practice but is limited in its ability to convince patent-holding companies to include developing countries which are at the

forefront of bearing the impact of the TRIPS agreement. Voluntary licences negotiated under the Medicines Patent Pool are publicly disclosed and include a far higher number of countries in the licence, although many middle-income countries have been excluded. Terms and conditions are better suited to foster generic competition within the geographic scope of the agreement. However, many companies holding patents on key medicines have refused to enter negotiations, or have not concluded licensing agreements with favourable terms and conditions with the Medicines Patent Pool.

The impact of VLs signed by Brazil is also concerning. Brazil has taken a different approach to the countries which have recently issued compulsory licences (e.g. India, Thailand, Ecuador and Indonesia), by focusing on developing partnerships with originator companies through voluntary licensing, with the goal of technology transfer and development of local capacity. But the impact of

this policy on access to medicines remains questionable.

A recent technology transfer licensing agreement signed between the government of Brazil and Bristol-Myers Squibb (BMS) for the local production of atazanavir, for example, is not expected to lead to significant price reductions. Indeed, the deal sets a price bar allowing only a 5% price reduction, in addition to a 4.5% royalty payment to BMS over the sales of any generic versions. Furthermore, although the drug requires boosting with RTV (and 45,000 people in Brazil take ATV, mostly boosted with RTV), the BMS licence does not allow for both drugs to be produced together as a fixed-dose combination (ATV/r).

A more comprehensive access framework that also involves the proactive use of TRIPS flexibilities, such as compulsory licensing, would likely be more effective in lowering the cost of medicines in the interest of public health.

SOUTH AFRICA'S PATENT LAW STILL ALLOWING FAR TOO MANY DRUGS TO BE PATENTED:

South Africa's patent regime is having a significant adverse impact on the affordability and accessibility of medicines for South Africans. The country has an estimated 5.6 million people living with HIV – more than any other nation.¹⁶ Yet while countries like Brazil and India have crucial safeguards built into their national patent systems in the interest of public health, South Africa's patent system and laws are outdated. The country grants an excessive amount of pharmaceutical patents and fails to stop pharmaceutical companies from indulging in evergreening. Patents are granted without substantive review, and no measures such as compulsory licences are employed when patented

drugs are expensive and unavailable for those who need them. In 2008 alone, South Africa granted 2,442 patents on pharmaceuticals, compared to just 278 in Brazil over a five-year period from 2003 to 2008.¹⁷

An example of the potentially harmful impact of South Africa's patent law is illustrated by secondary patents on ritonavir (RTV), a key drug needed to boost a number of protease inhibitors (DRV, ATV, LPV). The owner of secondary patents on RTV, AbbVie/Abbott could prevent the availability of the fixed-dose combination of ATV/r in South Africa, as well as hinder the development and use of

child-friendly formulations based on RTV, currently under development by the Drugs for Neglected Diseases *initiative* and Cipla.²⁰

South Africa-based Treatment Action Campaign (TAC) and MSF have together launched the 'Fix the Patent Laws' campaign, which is advocating for the South African government's revision of its laws to address urgent needs for affordable medicines and generic competition.¹⁸ The government has indicated it intends to make changes to its patent law through a new intellectual property policy, but has been slow to develop the policy and share it for public comment.¹⁹

LDCS GAIN REPRIEVE BEFORE NEEDING TO COMPLY WITH TRIPS, BUT THREAT REMAINS

Least-Developed Countries (LDCs), most of which are in sub-Saharan Africa, suffer from multiple disease burdens, including a significant prevalence of HIV/AIDS. Given these substantial health challenges, and given their level of development, LDCs were granted a temporary reprieve, known as a transition period, before having to meet their obligations under international trade rules.

In June 2013, a transition period allowing LDCs to avoid introducing some IP rules related to their membership in the WTO was set to expire. In advance of the deadline, LDC members of the WTO requested an extension that would enable them to remain exempt from implementing nearly all provisions of the TRIPS agreement, including for pharmaceutical products, until they are no longer classified as 'least-developed'.

In the face of opposition led by the United States and EU, a compromise was developed. WTO members agreed to extend the deadline by eight more years. MSF views the compromise as unsatisfactory in that the exemption is still time-bound (until 1 July 2021), instead of applying for as long as a country is classified as 'least-developed'. By refusing to grant them a longer and more complete extension, the US and EU are deliberately ignoring the health challenges faced by LDCs.

Given these shortcomings, MSF urges LDCs to request a more comprehensive extension (i.e. not time bound and without being subject to any binding or non-binding conditions), before the exemption period specifically related to pharmaceutical products (granted in 2002) comes to its end on 1 January 2016.

Critically, LDCs are also in a position to roll-back existing level of IP protection to meet domestic policy objectives. This is significant progress, as under the previous extension decision, LDCs were not allowed to roll-back IP laws. LDCs are now in a position to roll-back existing level of IP protection to meet domestic policy objectives, and should do this in the years ahead. Securing an extension will also be important as it would allow LDCs to develop pharmaceutical capacity and fill an important pharmaceutical niche by manufacturing new medicines now patented in key producer countries (such as India), which were required to achieve TRIPS-compliance in 2000 or 2005.

Beyond the lost opportunity, there are serious concerns that the US and EU will place tremendous pressure upon LDCs to accept a harmful compromise in 2016 that will limit access to affordable, generic medicines.

PAEDIATRICS IN FOCUS

Regimen consolidation: The 2013 WHO guidelines consolidate treatment recommendations for children. This is a step in the right direction for the paediatric ARV market, which has a long history of fragmentation, caused in part by too many regimen options for children.

The guidelines now recommend a LPV/r protease inhibitor-based regimen for all children under three years of age, combined with either AZT/3TC or ABC/3TC, and a number of new formulations that correspond to these recommendations are in the pipeline. For children starting treatment above three years of age, EFV should be used instead of LPV/r. Treatment for adolescents is harmonised with that for adults (and is based on TDF).

Newer, better formulations in the pipeline: Today, the only formulation of LPV/r available is a 42% alcohol-based solution that is extremely foul-tasting. In 2012, the Drugs for Neglected Diseases *initiative* (DNDi) and Indian drug manufacturer Cipla announced a collaboration to develop two protease inhibitor-based fixed-dose combinations for children, AZT/3TC/LPV/r and ABC/3TC/LPV/r.²⁰

These formulations will take the form of heat-stable solid granules, will taste better, and will be easily given with food, milk, breast milk or water. They will also allow easy dosing across weight bands. These products are expected to be available by 2015. In addition, DNDi is developing ritonavir heat-stable granules for children co-infected with TB who need additional boosting while on LPV/r treatment. Cipla is also developing a LPV/r-only sprinkle/ minitab formulation, registration of which is expected by early 2014.

The transition of the CHAI/UNITAID partnership on paediatric ARVs into a procurement consortium:

While regimen consolidation will help concentrate the paediatric market, the phasing out of a project aimed at bolstering the paediatric ARV market represents a significant threat to the stability of the market for child-formulations of ARVs. The CHAI/UNITAID paediatric partnership, launched in 2006, aimed to secure a more robust market for child-adapted ARVs by consolidating demand from beneficiary countries.²¹ With the project coming to an end by the close of 2013, all but four beneficiary countries have

transitioned to other funding sources. In light of the fact that the market for paediatric ARVs and the volumes ordered continue to be small, there is a need to secure the progress achieved and to expand the scope of this initially donor-driven project to the government procurement level. Consolidating demand and ensuring predictable ordering of paediatric formulations across procurement agencies and countries will help ensure that manufacturers remain interested in this small market.

Discordance among donors with regard to quality-assurance a further risk to market:

Another threat to the market consolidation for paediatric ARVs lies in the fact that different agencies funding ART in developing countries rely on different quality-assurance mechanisms for procurement. For example, the US government's PEPFAR programme relies not on WHO prequalification, but instead on US Food and Drug Administration approval. This can prove problematic for the effort to have a harmonised introduction of new and better-adapted paediatric products, which may be quality-assured by different bodies.



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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 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.

WHO recognises the evaluation of generic products by regulatory authorities that apply stringent standards for quality, similar to those recommended by WHO, such as, but not limited to, the US Food and Drug Administration (US FDA), the European Medicines Agency (EMA) and Health Canada.

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 antiretroviral drugs.

According to this scheme, products are "tentatively approved by US FDA". This means that although existing patents and/or other exclusive rights prevent marketing of the product in the US, the product meets all of the US FDA's safety, efficacy, and quality standards required for marketing in the US. Upon expiry of the patent protection or other exclusive rights in the US, tentatively approved products will be authorised for marketing in the US.

It should be noted that although WHO prequalification system recognises the US FDA "tentative approval" scheme under PEPFAR, the contrary does not apply. Only generic products that have a tentative approval by the US FDA are eligible for procurement under PEPFAR.

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.

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.

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 2013), 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 and the US FDA Approved and Tentatively Approved Antiretrovirals for the latest list of prequalified products and for information on ongoing assessments.



METHODOLOGY

Questionnaires were sent to both originator and generic companies manufacturing 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 March 2013.

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 Programme or US FDA on the date of requesting price information were included in this publication. Initial questionnaires were sent to companies in February 2013.

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 ART, such as diagnosis, monitoring or treatment of opportunistic infections.
- The manufacturers provide the prices listed in this publication. The prices paid by the purchaser might be higher because of additions (such as import taxes and distribution mark-ups), or may be lower as a result of effective procurement procedures or after negotiations. Therefore the document should not be viewed as a manufacturers' price list.
- Companies use different trade terms (known as incoterms). These incoterms 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 'Abbreviations' section in the annexes. For each company, the incoterms are reported in Annex 2.
- Companies have different eligibility criteria for differential pricing, meaning not all countries and not all entities (governments, NGOs, private sector bodies, etc.) can access the prices that are specified in this report. For each company, more detailed information on the different eligibility criteria is provided in Annex 2.
- The Clinton Foundation's Health Access Initiative (CHAI) 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 for both paediatric and adult formulations. The current CHAI price list can be found in Annex 5.
- 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.

HOW TO READ THE DRUG PROFILES

GENERAL INFORMATION

This section includes the history of the product (first approval, originator company and brand name), relevant WHO guidance, world sales of the originator and basic patent information.

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

PRICE

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.

Prices are rounded up to the third decimal for unit price and to the nearest whole number for yearly price per patient (ppy).

The annual cost of treatment per patient year has been calculated according to the WHO dosing schedules 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.

PAEDIATRICS

Within the tables, paediatric formulations are shaded in order to allow an easier distinction between adults and paediatric formulations.

For paediatric treatments, prices are calculated for a 10kg child using recommended dosing based on the 10 to 10.9kg weight band, as it appears in the WHO paediatric antiretroviral treatment guidelines.

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.

CATEGORIES 1 AND 2 – ACCESS TO PRICE DISCOUNTS

Each originator company applies different eligibility criteria to determine who can access its discounted prices on ARVs. 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. When companies provide two different tiers of discount, the countries eligible for the lowest price are grouped as 'category 1' and countries eligible for a discounted price that is not the lowest price are grouped as 'category 2'.

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 Annex 2.

QUALITY

Products quality-assured by WHO Prequalification Programme or US FDA (as of May 2013) 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 and the US FDA website for approved and tentatively approved ARVs, as these lists are updated regularly.

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.

The graph shows the lowest-priced generic product which is quality-assured by WHO Prequalification Programme or US FDA.

SPOTLIGHT ON ACCESS ISSUES

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.

Additional sections have been included to discuss and highlight specific issues with regard to WHO guidelines, paediatrics and patents.



ABACAVIR (ABC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2013 WHO Guidelines: ABC is recommended for infants and children as the preferred NRTI for first-line treatment and second-line treatment if a thymidine analogue was used in first-line. For adults, other treatment options are preferred, and ABC is part of an alternative regimen only.²²
- 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 approved by US Food and Drug Administration (FDA): December 1998.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2009: US\$160 million; 2008: \$175 million; 2007: \$215 million; 2006: \$230 million; 2005: \$268 million; 2004: \$290 million.
- Patents: GSK applied for the basic patents on ABC in 1989³¹ and 1990,³² and these expired in 2009 and 2010 respectively. To extend its patent monopoly, GSK subsequently applied for additional secondary patents related to new intermediates in 1995,³³ to the hemisulfate salt of ABC in 1998,³⁴ and to compositions of ABC particularly relevant for paediatric use in 1999,³⁵ which are due to expire in 2015, 2018 and 2019 respectively.

After 2010, sales not reported in the company's annual report.^{26, 27, 28, 29, 30, 31}

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

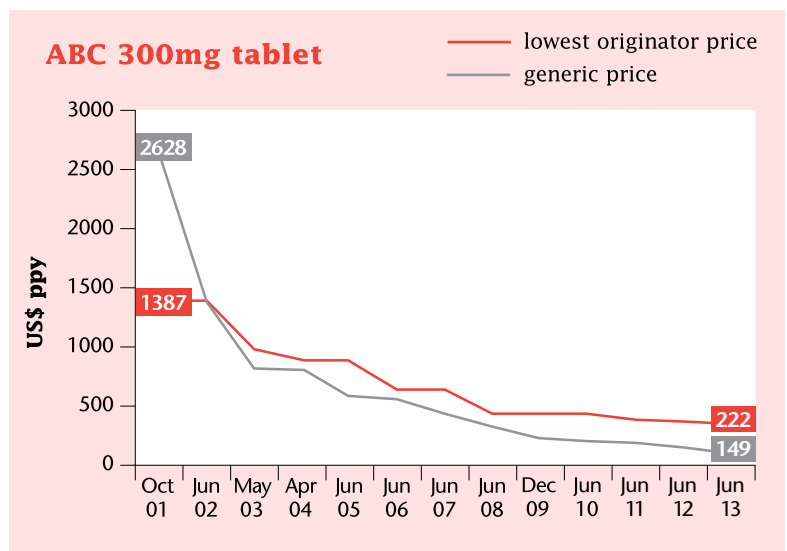
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aspen	Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides
ABC 20mg/ml oral solution (paediatrics)	12 ml	355 (0.081)	96 (0.022)	237 (0.054)	173 (0.040)	158 (0.036)			
ABC 60mg tablet (paediatrics)	4				146 (0.100)		122 (0.083)		
ABC 300mg tablet	2	222 (0.304)	172 (0.236)	152 (0.208)	170 (0.233)	153 (0.210)	149 (0.204)	189 (0.258)	256 (0.350)

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

As of May 2013, six generic sources of ABC 300mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 84%, while the generic price has dropped by 94%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

Affordability remains an issue with ABC, despite the 94% decrease in price of the generic version since 2001. The current lowest generic price for the 300mg tablet is still more than double the lowest generic prices of TDF 300mg and AZT 300mg.

WHO Guidelines

ABC can be used for adults as a potential alternative NRTI in some situations, but it adds complexity and cost, without clinical advantage.²²

ABC is recommended for children younger than three years of age as one of two preferred first-line NRTI options. ABC is the preferred first-line ARV for children over three years of age. If ABC was not used as a first-line component regimen, it is the preferred second-line treatment option for infants and children.²²

Paediatrics

The 60mg tablet remains expensive, despite the price of the lowest generic version having decreased from US\$134 ppy in 2011 to \$122 ppy in 2013, with no change in the price from 2012. Although there are three quality-assured sources of ABC 60mg tablets, supply issues remain, as the global demand is too low for manufacturers to produce this product.

ABC 60mg is also combined in a paediatric fixed-dose combination with 3TC 30mg tablet; the lowest reported price is \$128 ppy. Please refer to the ABC/3TC drug profile.

Patents

GlaxoSmithKline (GSK) could not apply for basic patents on ABC in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement, such as India. In addition, the basic patents on ABC have now expired in China.³⁶

GSK applied for patents on the hemisulfate salt of ABC in India but withdrew this application in October 2007 after civil society groups filed a pre-grant opposition.³⁷ GSK also applied for a patent on the oral solution of ABC, used particularly in paediatric regimens, which was granted in December 2007.³⁸ This patent raised concerns over continued generic availability of the ABC paediatric formulation, although the paediatric composition patent has not been used by GSK to block production of generic ABC/3TC for children in India.

As a result, both adult and paediatric versions of ABC/3TC are being produced by Indian generic manufacturers, and are available for export to developing countries. However, some developing countries are faced with intellectual property barriers (such as patents and/or data exclusivity terms) when seeking to use more affordable generic versions. These include:

- Patents on a paediatric composition granted in ARIPO countries, although these applications do not currently seem to be enforced;
- Patents on the hemisulfate salt, filed by GSK in China in May 1998, granted in 2008, and which will effectively block generic versions until 2018. Similar patents have been granted in OAPI and ARIPO countries,³⁹ although these applications do not currently seem to be enforced;
- Patents being aggressively enforced by GSK in Ukraine. In August 2012, GSK filed a claim to stop patent infringement on hemisulfate salt formulations against four Ukrainian companies and distributors, who had submitted bids to the Ministry of Health to supply ABC for adults. In addition, GSK filed an injunction to prohibit these companies from

selling and importing generic ABC from Cipla and Matrix (Mylan), which was granted in August 2012. The patent infringement claim is currently being considered by the Kiev commercial court.⁴⁰ This litigation may ultimately have a chilling effect on suppliers of generic ABC in Ukraine.

Mechanisms – voluntary or compulsory – may therefore be needed to overcome patent barriers. Some have already been taken:

- In a more conservative use of methods to facilitate access to medicines, Brazil negotiated reduced prices for ABC from GSK,⁴¹ although 20mg/ml formulation is not patented and was supplied by Indian manufacturers through a partnership with UNICEF.
- In September 2012, the Indonesian government issued compulsory licences on several key ARVs including ABC. This licence will last until the end of patent period in May 2018.⁴²
- In February 2013, the Medicines Patent Pool (MPP) and ViiV announced a licence agreement on paediatric ABC in 118 countries (see Annex 3).⁴³ This is ViiV's first and only licence with the MPP and provides the broadest geographical scope than any other voluntary licence. The adult formulation of ABC is not included in the licence and the patent will expire only after 2018 in many countries. Middle-income countries such as Brazil, China, Mexico, Peru, Russia, Uruguay, Ukraine and Venezuela are excluded from the licence agreement. GSK's enforcement of patents in Ukraine detailed above illustrates how exclusion from the geographical scope of this licence can pose problems for access to medicines in these countries.



ATAZANAVIR (ATV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI). ATV should always be boosted with ritonavir (RTV).
- 2013 WHO Guidelines: Boosted ATV is one of two preferred second-line treatment options for adolescents and adults. ATV boosted with RTV is an alternative second-line for children over six years of age who are failing NNRTI-based regimens.²²
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approved by US Food and Drug Administration (FDA): June 2003.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$1.5 billion; 2011: \$1.5 billion; 2010: \$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.^{44, 45, 46, 47, 48, 49, 50, 51}
- Patents: Novartis filed for the basic patent in April 1997 which is expected to expire in April 2017.⁵² BMS is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998⁵³ and on the process for preparing the bisulfate salt and novel forms in 2005.⁵⁴

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Bristol-Myers Squibb		Emcure	Hetero	Mylan
		Category 1 countries	Category 2 countries			
ATV 100mg capsule	xx*			(0.267)		
ATV 150mg capsule	2*	412 (0.564)	412 (0.564)	268 (0.367)		
ATV 200mg capsule	xx*	(0.677)	(0.677)	(0.483)		
ATV 300mg capsule	1*			268 (0.733)	256 (0.700)	195 (0.533)

* The dose of ATV must be boosted with RTV 100mg once a day.

Continued overleaf ⇨

SPOTLIGHT ON ACCESS ISSUES

For the first time, the prices for ATV 150mg and 200mg capsules quoted by Bristol-Myers Squibb (BMS) are the same for Southern African countries as for other sub-Saharan countries. This leaves Southern African countries paying 12% more than in 2012. It should be noted however that BMS's differential pricing structure of Category 1 and Category 2 is limited to sub-Saharan Africa and low-income countries, leaving middle-income countries outside sub-Saharan Africa without any tiered price discount and therefore subject to a case-by-case pricing approach. This can result in prohibitive prices, such as Brazil, which pays for BMS's ATV more than \$1,000 ppy.⁵⁵

In November 2011, Mylan became the first – and so far, only – manufacturer to have a US FDA tentatively approved source of boosted heat-stable ATV. Please refer to the ATV/r drug profile for further information on this combination.

For people co-infected with tuberculosis (TB), ATV cannot be used with rifampicin. Access to rifabutin therefore needs to be secured, preferably in a fixed-dose combination.

WHO Guidelines

ATV boosted with RTV is one of two PIs recommended for second-line treatment, to be taken with two NRTIs in adolescents, adults, pregnant women, and people co-infected with TB or hepatitis B (HBV).

ATV/r is recommended for second-line treatment for children over six years of age, when they are failing a NNRTI-based first-line regimen.²²

Paediatrics

ATV was approved for use in children between six and 18 years of age by the US FDA in March 2008. Paediatric formulations exist as 100mg, 150mg and 200mg capsules, and one generic company quoted a price for this year for WHO-prequalified versions.

Patents

In most developing countries with generic pharmaceutical production capacity, including Brazil, China and India, Novartis and BMS have filed patent applications related to the ATV compound,⁵⁶ the bisulphate salt,⁵⁷ the best route to making ATV,⁵⁸ and the combination of ATV with other ARVs.^{59, 60, 61, 62} Most of these 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

opposition⁶³ on Novartis's basic patent application⁶⁴ on the grounds of lack of novelty. The patent application has since been abandoned⁶⁵ but several divisional patent applications^{66,67} have been filed by Novartis. In addition, a patent application was filed by BMS in 2006, covering the most efficient route of manufacturing ATV and its bisulphate salt.⁶⁸ The application was opposed by generic companies, with the patent office subsequently rejecting the application.⁶⁹ However, BMS had already filed a divisional patent application,⁷⁰ which has been opposed by Cipla. These divisional and other patent applications on ATV and its use in combination with other ARVs^{71, 72, 73, 74} warrant additional pre-grant oppositions.⁷⁵

BMS has signed a number of voluntary licence agreements (see Annex 3 for more details):

- In February 2006, BMS granted technology transfer and voluntary licences to generic companies Emcure and Aspen to manufacture and sell ATV. In February 2008, Emcure received US FDA tentative approval for 100mg, 150mg and 200mg ATV capsules. Under the terms of the licences, sales of these products are royalty-free, but restricted to sub-Saharan Africa.

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- BMS has a separate agreement with Emcure that covers India,⁷⁶ even though licensing agreements should not be necessary for India if patent oppositions are successful in the country. If patents are granted, however, India and other countries may have to 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.
- In June 2011, BMS signed an immunity-from-suit agreement with Mylan enabling the generic company to manufacture and sell ATV in sub-Saharan Africa and India.⁷⁷ Like other voluntary licences, full terms and conditions of this agreement are not known and evaluating its actual impact on access and price competition is very difficult. In July 2012, BMS filed a case against Mylan in a US District Court, alleging that Mylan had breached its immunity-from-suit agreement by supplying over a year's supply of ATV to Venezuela through the Pan-American Health Organization (PAHO). BMS estimates lost profits on sales to be in excess of \$15 million. Furthermore, BMS

claims that as a consequence of Mylan's actions, its "negotiation strength with the Venezuelan government going forward has been severely damaged."⁷⁸ While this case is still pending it highlights the limitations of voluntary licensing mechanisms and that how generic companies should carefully consider their options before signing such licensing deals.

- In Brazil, where the patent on ATV doesn't expire until 2017, BMS's monopoly led to shortages of ATV in 2005⁷⁹ and 2011⁸⁰ with several people forced to change treatment regimens. Civil society groups urged the government to issue a compulsory licence (CL) arguing Brazilian law justified the measure.⁸¹ After the 2011 shortage, however, rather than issuing a CL for more affordable generic versions, the government announced the creation of a public-private partnership with BMS for local production of ATV.⁸² The reasons for this choice remain unclear and civil society groups continue to demand transparency over the contractual terms and conditions of this agreement, particularly since it involves Farmanguinhos, a publicly-owned laboratory.

In October 2012, a licensing agreement between Farmanguinhos and BMS was approved by the Brazilian Ministry of Health⁸³ for enabling technology transfer and generic production of ATV. Under the terms of the agreement, all of the Ministry of Health's needs for ATV will be supplied by BMS for the first three years, and for the following two years, BMS and Farmanguinhos will each cover 50% of Brazil's needs. The Ministry of Health expects Farmanguinhos to start local production in 2015, once all requirements regarding the registration of the generic version have been met.

Brazil currently pays \$2.80 for the 300mg formulation, but will pay BMS \$2.28 in 2016 once price reductions take effect as a part of the agreement. However, this price is almost four times more expensive than the lowest generic price available today. The prospective price for Farmanguinhos' generic version has not yet been made public, but BMS will be paid a 4.5% royalty.⁸⁴



ATAZANAVIR/ RITONAVIR (ATV/r)

GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- 2013 WHO Guidelines: Boosted ATV is one of two preferred second-line treatment options for adolescents and for adults. ATV/r is an alternative second-line for children over six years of age who are failing NNRTI-based regimens.²²
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Mylan's product was approved under the tentative approval scheme in November 2011.⁸⁵
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults.²⁴
- World sales of originator product: not applicable.
- Patents: Patents exist on the specific combination of ATV and RTV, as well as individual patents on ATV and RTV, which 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 unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Mylan
ATV/r 300/100mg tablet	1	219 (0.600)

SPOTLIGHT ON ACCESS ISSUES

In November 2011, the first generic source of ATV/r was WHO-prequalified and received US FDA tentative approval.

The introduction of a heat-stable formulation of ATV/r represents a step forward for access to second-line ARVs, as it represents the first fixed-dose combination alternative to heat-stable LPV/r, currently the most commonly used protease inhibitor. The ATV/r fixed-dose combination has the added benefit of reducing the pill burden – down from four pills a day for heat-stable LPV/r to one pill a day for ATV/r. At \$229 ppy, ATV/r is also more affordable in eligible countries than the lowest reported price of heat-stable LPV/r, which stands at \$265 ppy for Africa and least-developed countries.

However, there is a need for additional sources of ATV/r to ensure global supply does not rely on only one manufacturer. Additional manufacturers could also mitigate the impact of patent barriers or the reduced geographic scope of existing voluntary licences. At time of writing, WHO Prequalification was assessing a second generic source of ATV/r.⁸⁶

For people co-infected with tuberculosis (TB), ATV cannot be used with rifampicin. Access to rifabutine therefore needs to be secured, preferably in a fixed-dose combination.

WHO Guidelines

ATV boosted with RTV is one of two PIs recommended for second-line treatment, to be taken with two NRTIs in adolescents, adults, pregnant women, and people co-infected with TB or hepatitis B (HBV).²²

ATV/r is recommended for second-line treatment for children over six years of age, when they are failing a NNRTI-based first-line regimen.²²

Paediatrics

ATV was approved for use in children between six and 18 years of age by the US FDA in March 2008.²³

ATV requires boosting with RTV; there are currently no prequalified generic fixed-dose combination combining the two drugs available for children.

Patents

Please refer to the ATV and RTV drug profiles for details of patents on the individual drugs in this combination.

Abbott has for example 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.⁸⁷ In addition, a patent application filed by BMS on ATV/r is pending in India.⁸⁸

In June 2011, BMS signed an immunity-from-suit agreement with Mylan enabling the generic company to manufacture and sell ATV in sub-Saharan Africa and India (see Annex 3).⁸⁹ Like other voluntary licences, full terms and conditions of this agreement are not known to evaluate its actual impact on access and price competition. In addition, this agreement only covers a limited number of countries and patents may block access in other countries.

In Brazil, local production of ATV/r may be hampered by an agreement between Brazilian public laboratory Farmanguinhos and BMS (see the ATV drug profile for more information). The agreement includes technology transfer and local generic production of ATV but does not allow for production of other combinations that include ATV, such as ATV/r.



DARUNAVIR (DRV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2013 WHO Guidelines: Boosted DRV is indicated as an option for third-line treatment regimens.²²
- Originator company and product brand name: Janssen, Prezista. Janssen was formerly known as Tibotec and is a subsidiary of Johnson & Johnson.
- First approved by the US Food and Drug Administration (FDA): June 2006.²³
- WHO Model List of Essential Medicines (EML): Not included in the 18th edition for adults or the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$1.4 billion; 2011: \$1.2 billion; 2010: More than \$1 billion reported.^{90, 91}
- Patents: Searle and Monsanto applied for the basic patent in August 1993,⁹² which is due to expire in 2013. Subsequently, the US National

Institutes of Health (NIH) and the University of Illinois applied for patents more specifically related to DRV in 1999⁹³ and licenced them to Tibotec for development.⁹⁴ Tibotec later applied for patents related to improved forms and combinations of DRV. DRV patents related to key intermediates and combinations with ritonavir (RTV) and tenofovir (TDF) will expire in 2025.³⁹

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Janssen (J&J)	Aspen	Hetero
DRV 300mg tablet	4**	810 (0.555)	861 (0.589)	
DRV 400mg tablet	2*			730 (1.000)
DRV 600mg tablet	2**	810 (1.110)		1095 (1.500)

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

SPOTLIGHT ON ACCESS ISSUES

For the first time, Janssen has provided a price for DRV 600mg tablet, as this dosage strength is expected to eventually replace the 300mg tablet formulation.

Two generic companies provided prices for DRV, but both are yet to be approved by WHO Prequalification or a stringent regulatory authority (SRA). Hetero's 400mg and 600mg DRV tablets were however granted approval

by the Global Fund Expert Review Panel – a temporary approval for products awaiting WHO prequalification or SRA approval – making this the first third-line generic ARV available as an option for donor-driven procurement. The list of countries eligible for these prices under Hetero's licence with Janssen has not been disclosed.

Emcure's DRV 600mg tablets are also currently available in India.

This product will be submitted for SRA approval within the coming year or two, after which it will be available in certain countries, based on the conditions of the licence signed with Janssen.⁹⁵

DRV requires boosting with RTV – but there are currently no fixed-dose combinations combining the two drugs for either adults or children.

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WHO Guidelines

Boosted DRV, together with ETV and RAL, is recommended as an option for adults failing second-line treatment. However, DRV boosted with RTV can be used as an alternative PI option in second-line treatment and also in HIV-2 infection.²²

DRV is recommended as an option for children over three years of age failing second-line treatment.²²

Paediatrics

In December 2011, DRV was approved for use in children between three and 18 years of age. Paediatric formulations exist as an 100mg/ml oral suspension and in 75mg and 150mg tablets. No company provided a price for paediatric formulations.

DRV must be given with a RTV booster; however the only currently available paediatric RTV solution is not adapted for children, as it has a bitter aftertaste and contains 43% alcohol. The WHO Paediatric Antiretroviral Working Group considers the development of a fixed-dose combination containing DRV and RTV to be a high priority, though it is still unclear what the ratio of the co-formulation will be.

There is a need for studies in children under three years of age.²²

Patents

The basic patent related to DRV⁹⁶ could not be applied for in India as the country did not grant product patents on pharmaceuticals in 1994. After the implementation of the TRIPS agreement in 2005, which obliged India to accept product patent applications, Janssen (Johnson & Johnson) applied for several secondary patents in India related to the pseudo-polymorphic form,⁹⁷ the method for preparation of key intermediates of DRV⁹⁸ and combinations with RTV,⁹⁹ and with both TDF and RTV.¹⁰⁰ Pre-grant oppositions were filed against all of these applications.¹⁰¹ The Indian patent office has rejected several

applications related to the pseudo-polymorph,¹⁰² the method for preparation of key intermediates and the combination of DRV with RTV.¹⁰³ Other applications have been opposed by generic manufacturers. The patent application on the combination of DRV with TDF was withdrawn after opposition.¹⁰⁴

The patent threat to the combination of DRV with RTV nevertheless remained, as Janssen filed a divisional application,¹⁰⁵ which has since been abandoned after a pre-grant opposition by a generic manufacturer.¹⁰⁶ In addition, Abbott has filed patent applications on RTV in India and other developing countries which are pending – if granted, these would block the development of generic DRV/r combinations. To avoid this threat, the Delhi Network of Positive People has filed a patent opposition on the only remaining RTV application in India.

In China, Janssen 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.³⁶ Four DRV-related patents have been granted in South Africa.³⁹ 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 ppy when boosted with RTV, it is very expensive.

In September 2010, the US National Institutes of Health (NIH) licenced patents on DRV to the Medicines Patent Pool.¹⁰⁷ The move demonstrated political backing for the Pool and was also significant in that all developing countries were covered in the geographical scope of the licence. The NIH patent will

not free the way for generic versions of DRV in all developing countries, however, because additional patents are held by Janssen. In December 2011, the company announced its decision not to enter into negotiations to license its HIV drugs portfolio, including DRV, to the Pool.¹⁰⁸ In doing so, it has effectively made the NIH licence useless for manufacture and export to countries where it holds a patent.

Janssen is, however, engaging in voluntary licensing with two generic companies – Aspen in South Africa (only for packaging and distribution) and Emcure in India.¹⁰⁹ The terms of the licences are not public. In addition, the geographical scope is limited and exclude many low- and middle-income developing countries, where the price can reach over \$13,100 ppy. With patent restrictions in place, robust generic competition will not be possible until Janssen is ready to consider more open and transparent licensing mechanisms.

In June 2011, Janssen announced that it had entered into a licence agreement with Gilead for the development and commercialisation of a new once-daily single tablet fixed-dose combination containing DRV and Gilead's cobicistat. Subject to regulatory approval, Janssen will be responsible for the formulation, manufacture, registration, distribution and commercialisation of the DRV/cobicistat combination worldwide. Gilead retains sole rights for the manufacture, development and commercialisation of cobicistat as a stand-alone product and for use in combination with other agents.

See Annex 3 for more details on voluntary licences.



DIDANOSINE (ddl)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2013 WHO guidelines: ddl can be used as a potential NRTI back-up option in special situations, but it adds complexity and cost, without clinical advantage.²²
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Videx and Videx EC.
- First approved by US Food and Drug Administration (FDA): October 1991 for chewable tablets; October 2000 for enteric-coated capsules.²³
- WHO Model List of Essential Medicines (EML): Enteric-coated capsules are included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2005: US\$174 million; 2004: \$274 million; 2003: \$354 million. After 2005, sales are not reported in the company's annual report.¹¹⁰
- Patents: Although the basic patent on ddl filed in 1985 by the US National Institutes of Health (NIH) has expired, BMS holds patents on enteric-coated formulation in some countries, which run until 2018.¹¹¹

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Bristol-Myers Squibb	
		Category 1 countries	Category 2 countries
ddl 2g powder for reconstitution (final concentration 10mg/ml) (paediatrics)	12ml	233 (0.053)	Case-by-case basis
ddl 25mg tablet (paediatrics)	6	256 (0.117)	Case-by-case basis
ddl 100mg tablet (paediatrics)	xx	(0.213)	Case-by-case basis

SPOTLIGHT ON ACCESS ISSUES

For this year's edition of Untangling the Web, price information on ddl was requested only for paediatric formulations. Due to the low demand for this product globally, almost all of the generic manufacturers are now no longer producing ddl, and only Bristol-Myers Squibb (BMS) chose to provide a price for publication. Prices have not changed compared to last year for the oral solution, 25mg and 100mg tablets.

WHO guidelines

ddl is recommended for children as a potential alternative NRTI as part of second-line treatment in some situations, but it adds complexity and cost, without clinical advantage.²²

Paediatrics

Paediatric formulations for younger

children include buffered tablets that come with a high pill burden, or a 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 kept for a maximum of 30 days.

Patents

No application claiming a patent on the 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 – such as Brazil, China, and in ARIPO and OAPI countries³⁹ – the importation of more affordable generic versions

from India is blocked. These patents will not expire before 2018.

In Brazil, the active ingredient is in the public domain which has allowed the government to locally produce generic ddl as a powder for oral solution.¹¹² However, the enteric-coated capsule remains under patent.

In June 2011, BMS signed an immunity-from-suit agreement with Mylan enabling the generic company to manufacture and sell ddl, but only in sub-Saharan Africa and India.⁷⁷ See Annex 3 for information.

In September 2012, the Indonesian government issued compulsory licences on several key ARVs including ddl. This licence will last until the end of patent period in August 2018.⁴²



EFAVIRENZ (EFV)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2013 WHO Guidelines: EFV is the preferred first-line treatment for children over three years of age, adolescents and adults. EFV is not indicated in infants below three years of age.²²
- Originator companies and product brand names: Bristol-Myers Squibb (BMS), Sustiva; or Merck, Stocrin.
- First approved by US Food and Drug Administration (FDA): September 1998.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$1.5 billion; 2011: \$1.5 billion; 2010: \$1.4 billion; 2009: \$1.3 billion; 2008: \$1.1 billion; 2007: \$956 million; 2006: \$791 million; 2005: \$680 million; 2004: \$621 million; 2003: \$544 million.^{44, 45, 46, 47, 48, 113, 114, 115}
- Patents: Merck filed the basic patent on EFV in 1993, which is due to expire in August 2013.¹¹⁶ Subsequently, Merck filed for patent applications related to crystallised forms, due to expire in 2018.¹¹⁷ Patents on combinations of EFV with emtricitabine (FTC) and tenofovir (TDF) were also filed by Gilead and do not expire before 2026.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Merck		Aurobindo	Cipla	Emcure	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides
		Category 1 countries	Category 2 countries									
EFV 30mg/ml suspension (paediatrics)	xx	(0.094)	Case-by-case basis									
EFV 50mg capsule (paediatrics)	xx			(0.075)				(0.073)				
EFV 50mg tablet (paediatrics)	xx	(0.114)	Case-by-case basis									
EFV 100mg dispersible tablet (paediatrics)	xx											
EFV 200mg capsule	3			77 (0.070)	73 (0.067)			66 (0.060)			63 (0.058)	
EFV 200mg tablet	3	394 (0.360)	Case-by-case basis									113 (0.103)
EFV 600mg tablet	1	237 (0.650)	Case-by-case basis	40 (0.110)	49 (0.133)	61 (0.167)	47 (0.130)	43 (0.117)	49 (0.133)	39 (0.106)	43 (0.117)	41 (0.112)

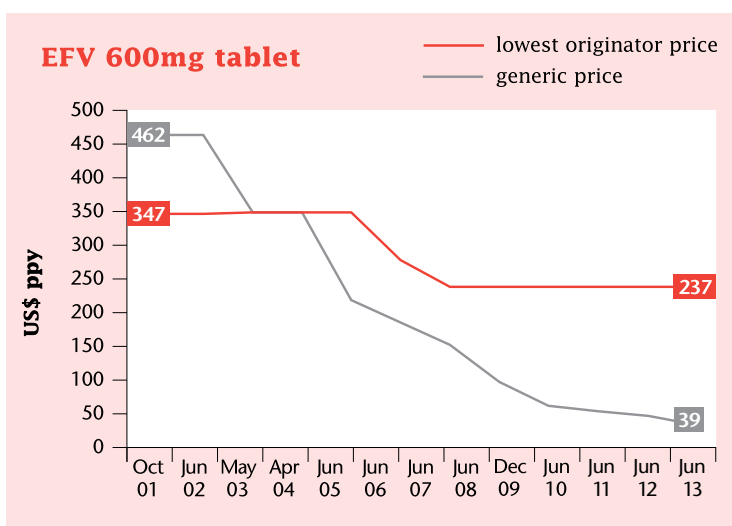
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❖ Efavirenz (EFV) continued

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

As of May 2013, nine generic sources of EFV 600mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2002, the originator price has decreased by 32% (but has not changed since 2007), while the generic price has dropped by almost 92%.



SPOTLIGHT ON ACCESS ISSUES

EFV is included in a number of fixed-dose combinations – please refer to those drug profiles for further information.

WHO Guidelines

EFV is the recommended NNRTI for first-line treatment for adolescents, pregnant and breastfeeding women, adults and people who are co-infected with tuberculosis (TB) or hepatitis B virus (HBV).

For children over three years of age, EFV is the recommended NNRTI for first-line treatment and is preferred for second-line, including for those who have failed an initial boosted PI regimen and those who are co-infected with TB. EFV is not recommended for infants and children below three years of age.²²

Paediatrics

There is an urgent need to establish the dosing of EFV for children younger than three years of age. In the absence of such data, treatment options for children remain limited, particularly for young children co-infected with TB who cannot be given NVP because of interactions between NVP and TB drugs.

In addition to the 200mg tablets and capsules, EFV is available as an oral

solution, produced only by Merck. WHO is calling for a double scored 600mg tablet to be produced, so that it can be broken into three 200mg tablets for use in paediatrics and for easier alignment with adult formulations.²²

Patents

EFV remains expensive in countries where Merck holds patents that block the production and sale of generics. In certain 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 started purchasing EFV at \$106 ppy – considerably lower than the previous price of \$511 ppy.^{118, 119}
- In May 2007, Brazil – after numerous unsuccessful negotiations with Merck – issued a compulsory licence to import more affordable generic versions 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 WHO-prequalified generic version for \$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched a locally produced generic version for use in the Brazilian health system.¹²⁰

- 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 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.¹²¹
- In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including EFV. This licence will last until the end of patent, in August 2013.⁴²



EMTRICITABINE (FTC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2013 WHO Guidelines: FTC is recommended for first- and second-line treatment for infants, children, adolescents, adults including patients who are co-infected with tuberculosis (TB) and hepatitis B (HBV).²²
- Originator company and product brand name: Gilead, Emtriva.
- First approved by US Food and Drug Administration (FDA): July 2003.²³
- WHO Model List of Essential Medicines (EML): Not included in the 18th edition for adults or the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$29 million; 2011: \$29 million; 2010: \$28 million; 2009: \$28 million; 2008: \$31 million; 2007: \$32 million; 2006: \$36 million; 2005: \$47 million; 2004: \$58 million.^{122, 123, 124, 125, 126, 127, 128}
- Patents: The basic patent on FTC and lamivudine (3TC) was filed by IAF Biochem in 1990 and expired in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.^{129, 130} Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.^{131, 132} These expired between 2010 and 2011. Gilead filed combination patents on FTC in several countries which expire in 2024 and 2026.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Cipla
FTC 200mg capsule	1	73 (0.200)

SPOTLIGHT ON ACCESS ISSUES

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²²

FTC is included in a number of fixed-dose combinations (FDCs) – please refer to those drug profiles for further information. According to the prices quoted by manufacturers, 3TC-based FDCs continue to be more affordable than FTC-based FDCs.

WHO Guidelines

FTC is recommended for first- and second-line treatment in combination with other ARVs in regimens for adolescents, pregnant and breastfeeding women, adults and people who are co-infected with tuberculosis (TB) or HBV.²²

Paediatrics

Currently, there are no paediatric fixed-dose combinations available which

include FTC. Paediatric FDCs containing 3TC do exist, however – please refer to the relevant drug profiles.

Patents

In 2005, Gilead acquired the royalty interest for FTC under a US\$525 million agreement with Emory University.¹³³

Basic patents on FTC could not be applied for in India because the country did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement. Gilead however has reported holding patent rights in 45 other developing countries.¹³⁴

In mid-2006, Gilead signed licensing agreements with generic manufacturers in India, allowing them to manufacture and export generic versions of TDF in combination with other ARVs, including FTC, to a limited list of

countries in return for the payment of a five per cent royalty.¹³⁵ In July 2011, Gilead subsequently signed a licence agreement with the Medicines Patent Pool authorising the Pool to sub-licence four of its antiretrovirals, including FTC, to manufacturers based in India.

While Gilead’s 2006 licence covers 95 territories, the 2011 licence covers 112 territories, including 45 developing countries where FTC patents are granted or filed. It is noteworthy FTC patent in these developing countries will not have a blocking effect because MPP’s 2011 licence contains a clause not to enforce FTC patents, allowing for the production of other fixed-dose combinations involving other licenced compounds.

For details on these and other voluntary licences, see Annex 3.



ETRAVIRINE (ETV)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2013 WHO Guidelines: ETV is indicated as an option for third-line treatment regimens.²²
- Originator company and product brand name: Janssen, Intelence. Janssen was formerly known as Tibotec and is a subsidiary of Johnson & Johnson.
- First approved by the US Food and Drug Administration (FDA): January 2008.²³
- WHO Model List of Essential Medicines (EML): Not included in the 18th edition for adults or the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$349 million; 2011: \$314 million; 2010: \$243 million.¹³⁶
- Patents: Janssen applied for the basic patent on ETV in 1999, which is due to expire in 2019.¹³⁷ In 2006, Tibotec applied for subsequent patents related to novel series of bisaryl substituted pyrimidine derivatives.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Janssen (J&J)	Aspen
ETV 100mg tablet	4	438 (0.300)	467 (0.320)

SPOTLIGHT ON ACCESS ISSUES

For the first time, a generic version of ETV is available; however it is currently more expensive than Janssen's product.

WHO Guidelines

ETV is indicated as a treatment option for adults and children over six years of age who are failing second-line regimens.²²

Paediatrics

Janssen (Johnson & Johnson) did not provide pricing information for the 25mg scored tablet that was approved for use in children by the US FDA in March 2012.

Patents

Patents have been widely applied for in the developing world, including

in Africa. Janssen obtained patents on the ETV molecule in ARIPO and OAPI countries,³⁹ in India¹³⁸ and in China.³⁶ This patent will not expire before 2019. In India, Janssen has filed additional patent applications on new forms which, if granted, will extend its monopoly in India from 2021 to 2027.^{139, 140}

These patents will block the development of generic formulations of ETV, unless voluntary or compulsory licences are issued. In August 2009, the company signed a royalty-free, non-exclusive agreement with Aspen and Emcure covering all of sub-Saharan Africa and least-developed countries for ETV.

This is not a manufacturing licence and under this agreement, Aspen and Emcure handle regulatory and distribution activities only. The terms are not public and the geographical scope is limited. For details on this and other voluntary licences, see Annex 3.

In December 2011, Janssen announced its decision not to enter into negotiations with the Medicines Patent Pool to licence its HIV drugs portfolio, including ETV.¹⁰⁸ With patent restrictions in place, robust generic competition will not be possible until Janssen is ready to consider more open and transparent licensing mechanisms.



LAMIVUDINE (3TC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2013 WHO Guidelines: 3TC is recommended for first- and second-line treatment for infants, children adolescents and adults.²²
- 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 approved by US Food and Drug Administration (FDA): November 1995.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$74 million; 2011: \$110 million; 2010: \$186 million; 2009: \$197 million; 2008: \$225 million; 2007: \$309 million; 2006: \$398 million; 2005: \$398 million; 2004: \$549 million.^{26, 29, 30, 31, 141, 142, 143}
- Patents: The basic patent on 3TC and emtricitabine (FTC) was filed by IAF Biochem in 1990 and expired in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Alkem	Aspen	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy	Strides
3TC 10mg/ml oral suspension (paediatrics)	10ml	171 (0.047)			28 (0.008)	30 (0.008)	37 (0.010)				
3TC 150mg tablet	2	75 (0.103)	44 (0.060)	26 (0.036)	27 (0.037)	30 (0.042)	26 (0.036)	24 (0.033)	29 (0.040)	24 (0.033)	28 (0.038)
3TC 300mg tablet	1					37 (0.100)		21 (0.058)	61 (0.167)		

Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

3TC is an equivalent alternative to FTC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²²

3TC is included in a number of fixed-dose combinations (FDCs) – please refer to those drug profiles for further information. According to the prices quoted by manufacturers, 3TC-based FDCs continue to be more affordable than FTC-based FDCs.

WHO Guidelines 2013

3TC is recommended for first- and second-line treatment for adolescents, pregnant and breastfeeding women, adults and people who are co-infected with tuberculosis (TB) or HBV.²²

3TC is recommended for first- and second-line treatment for infants and children, including those who are co-infected with TB or HBV.²²

Paediatrics

There are three WHO-prequalified generic sources of 3TC oral solution – the lowest reported price is \$28 ppy. There are very few paediatric fixed-dose combinations containing 3TC, however.

Patents

Patent barriers related to 3TC are limited as the basic patent expired in 2010 and there are several WHO-prequalified or FDA approved generic manufactures already making this drug. The only patent related barrier could be on combination patents as a new formulation patent is filed in many countries which will not expire before 2018.¹⁴⁴

As the molecular structure of FTC and 3TC are very closely related, the same patent covers both drugs. Generic competition for 3TC originated in countries with

manufacturing capacity where the drug was not under patent, such as India, Thailand and Brazil. In India, 3TC is being produced in combination with first-line ARVs and in combination with ABC as a paediatric dose. In China, several patents were granted on 3TC, one of which expired in 2011.

GSK obtained a licence from IAF BioChem International to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which expired in June 2012.¹⁴⁵ GSK also applied for a new formulation patent in 1998. This patent was granted in Brazil, China and in ARIPO and OAPI countries.¹⁴⁶

In November 2012, Ecuador issued a compulsory licence on key patents related to ABC and 3TC to manufacture of ABC/3TC. The licence was issued to Ecuadorean manufacturer Acroxmax, in a bid to reduce the cost by 75 per cent.¹⁴⁷



LOPINAVIR/ RITONAVIR (LPV/r)

GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- 2013 WHO Guidelines: LPV/r is recommended for first-line treatment for all HIV-infected children below three years of age (36 months), regardless of NNRTI exposure. LPV/r is also indicated for second-line treatment for children and adults.²²
- Originator company and product brand name: Abbott, Kaletra or Aluvia. In 2013, Abbott separated into two separate companies, Abbott and AbbVie, with the latter as research-based biopharmaceuticals company holding the portfolio for most medicines including Kaletra.
- First approved by US Food and Drug Administration (FDA): September 2000 for soft-gel capsules; October 2005 for heat-stable tablets.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$733 million, 2011: \$1.2 billion; 2010: \$1.3 billion; 2009: \$1.4 billion; 2008: \$1.5 billion; 2007: \$1.3 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million. 148, 149, 150, 151, 152, 153
- Patents: Most patents related to ritonavir (RTV) also cover LPV/r. Abbott applied for the basic patent related to LPV in 1996.¹⁵⁴ In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997, which are due to expire in 2017.¹⁵⁵ An application for a patent on the LPV/r heat-stable tablet formulation that is now widely used in developing countries was filed in 2004,¹⁵⁶ and it could potentially run until 2024.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

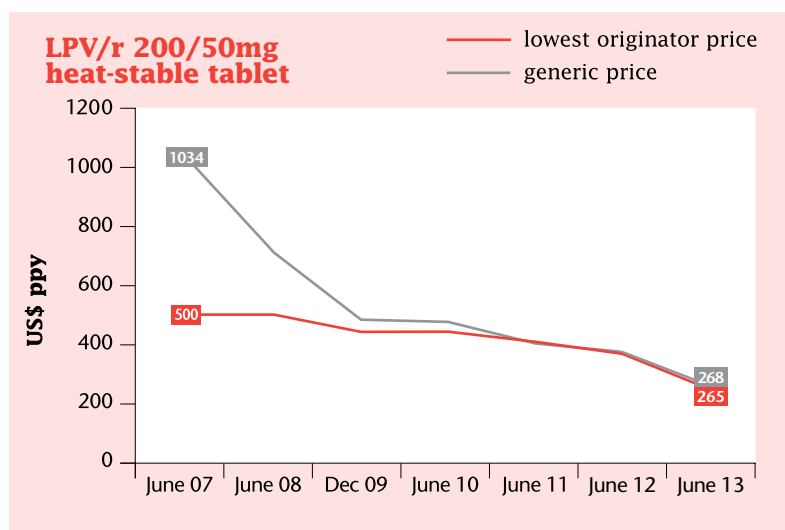
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	AbbVie (Abbott)		Aurobindo	Cipla	Hetero	Mylan
		Category 1 countries	Category 2 countries				
LPV/r 80/20mg/ml oral solution (paediatrics)	4 ml	147 (0.101)	296 (0.203)		292 (0.200)		
LPV/r 100/25mg heat-stable tablet (paediatrics)	3	108 (0.099)	278 (0.254)	150 (0.137)	183 (0.167)		
LPV/r 200/50mg heat-stable tablet	4	265 (0.182)	740 (0.507)	268 (0.183)	389 (0.267)	304 (0.208)	268 (0.183)

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

As of May 2013, four generic sources of LPV/r 200/50mg heat-stable tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

The price of the originator continues to be lower than the generic although the margin has been greatly reduced. Since last year's edition, both originator and generic prices have dropped by slightly more than \$100.



Continued overleaf ❖❖❖

SPOTLIGHT ON ACCESS ISSUES

LPV/r is currently the most commonly used protease inhibitor. The introduction of a heat-stable formulation of ATV/r – with a first generic source WHO-prequalified in November 2011 – represents a step forward for access to second-line ARVs, as it represents the first fixed-dose combination alternative to heat-stable LPV/r. ATV/r has the added benefit of reducing the pill burden – down from four pills a day for heat-stable LPV/r to one pill a day for ATV/r – and is priced more affordably. Please refer to the ATV/r drug profile for further information.

Although several WHO-prequalified generic sources of heat-stable LPV/r 200/50mg tablets exist, the most discounted price provided by the originator, AbbVie (Abbott), remains marginally more affordable. At time of writing, WHO Prequalification was assessing alternative generic versions of LPV/r 80/20mg/ml oral solution and LPV/r 100/25mg tablet.⁸⁶

WHO Guidelines

With ATV/r, LPV/r is one of two preferred boosted PI options for second-line ART for adults and children.²²

A LPV/r-based regimen is recommended as first-line ART for all children below three years of age, regardless of NNRTI exposure.²²

Paediatrics

Paediatric formulations exist, but are not adapted to the conditions of resource-limited settings. LPV/r solution requires refrigeration until it is dispensed, after which it must be stored below 25°C for no more than six weeks. It is also unsuitable for children due to its unpleasant taste and 42% alcohol content.

There is an urgent need for more adapted heat-stable paediatric formulations of LPV/r, such as soluble granules or sprinkles. The WHO Paediatric Antiretroviral Working Group considers the development of a LPV/r 40/10mg heat-stable sprinkle to be a high priority. An Indian generic company is developing such a sprinkle, which is expected to be submitted for stringent regulatory authority approval by the end of 2013.¹⁵⁷

Patents

Given the compound patent on LPV will not expire before 2016, the risk of patent related access barrier is high as the basic patent as well as several combination patents are granted/pending in developing countries. Abbott could not file a basic patent on LPV in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement, like India. Competition from generic sources from India has, together with the increase in global demand, brought down the price LPV/r.

However, the company applied for several other patents, including:

- on the polymorphic forms of LPV¹⁵⁸ and RTV.¹⁵⁹ The Indian patent office rejected a patent application on LPV crystalline polymorph.¹⁶⁰ Abbott also abandoned the application related to RTV crystalline polymorph and its divisional patent applications¹⁶¹ after patent oppositions were filed by civil society organisations and generic companies.
- on the combination of LPV/r in a tablet formulation.^{162, 163} Following a pre-grant opposition, this application was rejected by the Indian patent office.¹⁶⁴ Abbott also abandoned the two divisional patent applications that had been filed on the tablet formulation.^{165, 166}

- on the LPV process.^{167, 168} This application, and its divisional application,¹⁶⁹ have also been abandoned after patent oppositions were filed by generic manufacturers.¹⁷⁰
- and on the solid pharmaceutical dosage (tablet) formulation of RTV.¹⁰⁶ This is the only remaining patent application still under examination; a network of people living with HIV/AIDS filed a pre-grant opposition in 2012. If this patent application is granted, current generic competition on LPV/r – which continues to bring prices down substantially as demand has increased – will be under threat.

In Thailand, where Abbott holds patents on LPV/r and the drug cost \$2,200 ppy, the Ministry of Public Health issued a compulsory licence in January 2007 to import more affordable generic versions of the drug from India.¹¹⁸ Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies for the decision, with Abbott's response being to withdraw all registration applications for its new products in Thailand, including heat-stable LPV/r. Thailand today imports generic LPV/r from India for \$793 ppy.¹¹⁹

After Thailand issued the compulsory licence, Abbott reduced the price for both the soft-gel and heat-stable versions to \$1,000 ppy for 40 middle-income countries, including Brazil, which at the time was paying \$1,380 ppy.

In Brazil, government entered into negotiations with Abbott in 2005 to reduce the price of LPV/r;

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⋮ Continued from below left

in June of the same year, the Ministry of Health declared the drug to be of public interest – the first step towards issuing a compulsory licence. However, in October 2005, an agreement between Abbott and the government was signed.

The basic patent for LPV/r was 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 required by countries that are signatories of the TRIPS agreement. In 2007, the National Federation of Pharmacists – on behalf of the Brazilian Network for the Integration of Peoples – made a request to the Brazilian Prosecutor General to consider overturning the pipeline mechanism on the grounds that it was unconstitutional. A key argument in favour of overturning the mechanism was that these patents should not be granted in Brazil, since they were already in the public domain, and that granting patents in this manner is against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court,¹⁷¹ but the case has

not yet been heard.¹⁷² However, in February 2012, the Federal Court of Rio de Janeiro annulled the original patent granted in 1997 through the pipeline mechanism¹⁷³ following a nullity action filed by a generic manufacturer in September 2009.

The decision marked an important step to end the monopoly over LPV/r in Brazil, allowing for price reductions through generic competition. The decision by the Federal Court also has wider implications for access to medicines, as it sets a precedent to address long-standing concerns about the use of the pipeline process to grant patents in Brazil. Abbott has filed an appeal. Given the decision by the Supreme Court on the unconstitutionality case is still pending, the Federal Court decision currently provides an option for judges to address issues related to the pipeline mechanism on a case-by-case basis.

Abbott has made several other patent applications related to LPV/r in Brazil, some of which have been opposed by civil society groups and generic companies. In November 2011, Brazilian civil society groups opposed a patent covering the heat-stable tablet formulations of

both LPV/r and RTV.^{174, 175}

The move was an attempt to avoid monopoly extension over LPV/r and appropriation of stand-alone RTV, since this patent, if granted, would allow patent protection for both until 2024. The Brazilian patent office has said that it will fast track its analysis of the opposition.¹⁷⁶ In October 2012, the Brazilian government announced a partnership between Farmanguinhos, Furp and Iquego (all national public laboratories) for the local production of LPV/r.

In November 2011, several public health groups including Public Citizen launched a global campaign across 12 countries to challenge Abbott’s patents on LPV/r via patent oppositions or requests for compulsory licences. The campaign is aimed at spurring generic competition to lower the price of LPV/r. In Ecuador, where a compulsory licence was originally issued on RTV, the government is now evaluating a new licence request regarding the LPV/r patent.¹⁷⁷ In September 2012, the Indonesian government issued compulsory licences on several key ARVs including LPV/r. This licence will last until the end of patent in August 2018.⁴²



NEVIRAPINE (NVP)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2013 WHO Guidelines: NVP is recommended as an alternative first-line treatment for infants, children, adolescents and adults.²²
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune and Viramune XR.
- First approved by US Food and Drug Administration (FDA): June 1996.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2007: US\$412 million; 2006: \$370 million; 2005: \$386 million; 2004: \$378 million. After 2007, sales are not reported in the company's annual report.^{178, 179, 180, 181}
- Patents: BI applied for the basic patents on NVP in November 1990, which expired in November 2010.¹⁸² BI also was granted patents in 1998 on the hemihydrate form of NVP used in the suspension, which are due to expire in 2018.¹⁸³ Additionally, BI applied for a patent on the extended release formulation of NVP in 2008, which is due to expire in 2028.¹⁸⁴

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

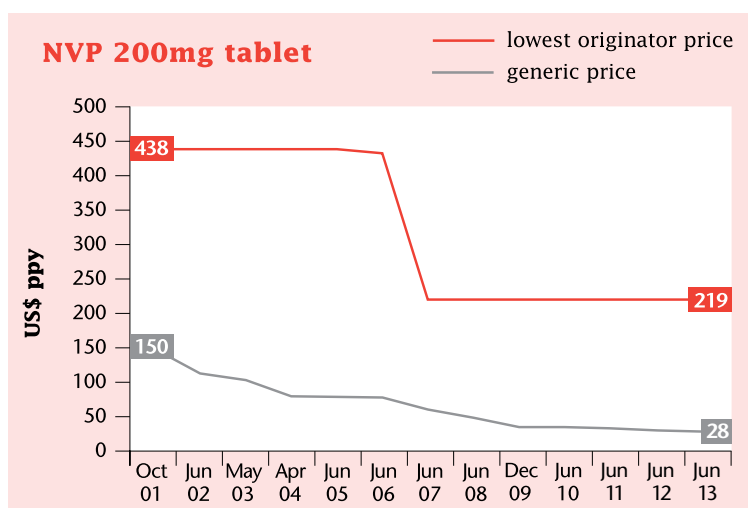
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Boehringer Ingelheim		Aspen	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides	Universal Corporation
		Category 1 countries	Category 2 countries										
NVP 10mg/ml suspension (paediatrics)	20ml	380 (0.052)	532 (0.073)		61 (0.008)	64 (0.009)							
NVP 50 mg tablet for oral suspension (paediatrics)	4				75 (0.052)	55 (0.038)							
NVP 200mg capsule	2												33 (0.045)
NVP 200mg tablet	2	219 (0.300)	438 (0.600)	31 (0.042)	28 (0.038)	33 (0.046)	32 (0.044)	29 (0.040)	29 (0.040)	44 (0.061)	30 (0.042)	29 (0.040)	

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

As of May 2013, several generic sources of NVP 200mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 50% whereas the generic price has dropped by 81%.



SPOTLIGHT ON ACCESS ISSUES

WHO Guidelines

NVP is an alternative first-line treatment option for infants, children, adolescents, pregnant and breast-feeding women, adults and people who are co-infected with hepatitis B virus (HBV).

In children under three years of age, if a LPV/r-based regimen cannot be used, treatment should be initiated with a NVP-based regimen, regardless of NNRTI exposure.²²

Although no longer recommended by WHO, single dose NVP continues to play a role in prevention of mother-to-child transmission (PMTCT) programmes globally.

NVP is included in a number of fixed-dose combinations (FDCs) – please refer to those drug profiles for further information.

Paediatrics

Currently, there are only two quality-assured generic sources of the paediatric oral solution of NVP; price continues to be an issue, with paediatric formulations much more expensive compared to those for adults.

At time of writing, WHO Prequalification is assessing several alternative generic sources of NVP 50mg and 100mg tablets, some of which are for oral suspension.⁸⁶

The WHO Paediatric Antiretroviral Working Group considers the development of a NVP 20mg scored tablet to be a high priority.²²

Patents

With NVP basic patent expired in 2010, some patent related barriers are still there due to secondary patents filed by Boehringer Ingelheim (BI) on extended release formulation and hemihydrate formulation. These patents are granted or filed in several countries and can block generic competition as they will not expire before 2028 and 2018 respectively.

In African countries, low-income countries and least-developed countries, BI has a non-assert policy for its patents, which overcomes some 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. See Annex 3 for details.

After India introduced patent protection for pharmaceutical products in 2005, BI applied for a patent on the hemihydrate form of NVP,¹⁸⁵ which relates to the paediatric suspension formulation. Civil society groups filed a pre-grant opposition to BI's application in May 2006, and in June 2008, the application was rejected by the Indian patent office,¹⁸⁶ 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.¹⁸⁷

In 2008, BI filed a Patent Cooperation Treaty (PCT) application for an extended release formulation of NVP¹⁸⁸ – in India the same application was published in 2010.¹⁸⁹ This application relates to the once-a-day dosing of NVP.



RALTEGRAVIR (RAL)

GENERAL INFORMATION

- Therapeutic class: Integrase inhibitor.
- 2013 WHO Guidelines: RAL is indicated as an option for third-line treatment regimens.²²
- Originator company and product brand name: Merck, Isentress.
- First approved by the US Food and Drug Administration (FDA): October 2007.
- WHO Model List of Essential Medicines (EML): Not included in the 18th edition for adults or the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$1.5 billion; 2011: \$1.4 billion; 2010: \$1.1 billion; 2009: \$752 million; 2008: \$361 million; 2007: \$41 million.
190, 191, 192, 193, 194
- Patents: The Institute for Research in Molecular Biology (IRBM), one of Merck's research sites, applied for the basic patent on RAL in October 2002.¹⁹⁵ This 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 2025.¹⁹⁶

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Merck	
		Category 1 countries	Category 2 countries
RAL 400mg tablet	2	675 (0.925)	Case-by-case basis

STOP PRESS:

At the time of going to press, the first generic raltegravir product became available for procurement based on quality assessment performed by the Expert Review Panel of Global Fund. The manufacturer, Hetero, was contacted but did not submit prices in time for inclusion in this report.

SPOTLIGHT ON ACCESS ISSUES

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

Currently, there is no generic version of RAL.

WHO Guidelines

RAL is indicated as an option for adults and children over two years of age who are failing second-line treatment.²²

Paediatrics

In December 2011, the US FDA approved dosing recommendations for RAL for paediatric patients aged two to 18 years of age and weighing at least 10kg. In addition, a 100mg scored chewable tablet and 25mg chewable tablet were approved for use in children.

Patents

Merck and IRBM applied for international patent applications^{197, 198, 199} under the Patent Cooperation Treaty (PCT) which facilitated the filing of these applications in many PCT member states, including some developing countries with generic drug manufacturing capacity like Brazil, China, India and South Africa.

In India, IRBM was granted a patent in December 2007 which will not expire until 2022.²⁰⁰ An application on the potassium salt of RAL is also pending for review before the Indian patent office²⁰¹ and a pre-grant opposition was filed in July 2011.²⁰² If granted, Merck's monopoly in India will be extended by an additional five years to 2027.

In 2011, Merck signed voluntary licences with two companies, Emcure and Mylan, to supply RAL to 60 sub-Saharan African and low-income countries. Significantly, although the voluntary licences were granted to Indian generic companies to produce and export RAL, India itself is excluded from the licences' geographical scope (See Annex 3 for details). RAL produced locally by the licencees cannot be marketed in India and is not available for procurement by MSF projects in India, which currently pay as much as \$1,667 ppy.

In Brazil, the Ministry of Health has announced that it is working on a technology transfer agreement with Merck for RAL.²⁰³ The terms of this agreement are not public. In 2010, the Brazilian government was paying \$5,870 ppy, a price that is expected to decrease to \$4,000 with the technology transfer in 2015.²⁰⁴

This approach – which is unlikely to ensure that prices are reduced to the same level 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 medicines 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 6,000 people taking RAL, the country is one of the largest developing country consumers of the drug²⁰⁵ and could thus stimulate an international generic market where prices are reduced through competition and economies of scale.



RITONAVIR (r or RTV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2013 WHO Guidelines: RTV is recommended as a booster for first-line treatment for children below three years of age and for second-line treatment as a booster for infants, children, adolescents and adults.²²
- Originator company and product brand name: Abbott, Norvir. In 2013, Abbott separated into two separate companies, Abbott and AbbVie, with the latter as research-based biopharmaceuticals company holding the portfolio for most medicines including Norvir.
- First approved by US Food and Drug Administration (FDA): March 1996 for the oral solution; June 1999 for capsules.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2004: US\$194 million; 2003: \$93 million; 2002: \$122 million. After 2004, sales are not reported in the company's annual report.²⁰⁶
- Patents: Abbott applied for the basic patent on RTV in 1993, which is due to expire in 2013–14.²⁰⁷ Subsequently, Abbott applied for patents related to polymorphic forms of RTV^{208, 209} and to a soft-gel capsule formulation.²¹⁰ These are due to expire in 2019 and 2020, respectively.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

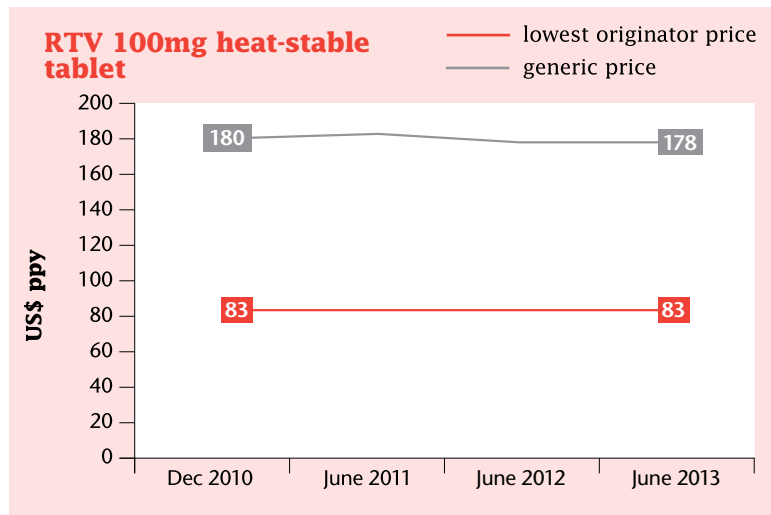
	Daily dose	AbbVie (Abbott)		Cipla	Mylan
		Category 1 countries	Category 2 countries		
RTV 80mg/ml oral solution (paediatrics)	xx	(0.091)	Case-by-case basis		
RTV 100mg heat-stable tablet	2*	83 (0.114)	Case-by-case basis	316 (0.433)	178 (0.243)

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

Evolution of the lowest price quoted for eligible developing countries since 2010:

As of May 2013, only one generic source of RTV 100mg heat-stable tablet is quality-assured by US FDA or WHO prequalification. Its price is shown here.

Since 2010, the generic price has stayed largely stable. The originator price is 53% lower than the generic price.



SPOTLIGHT ON ACCESS ISSUES

RTV is of crucial importance for the scaling-up and management of second-line treatment, as the vast majority of protease inhibitors must be boosted with this drug.

Despite there being several generic manufacturers producing heat-stable LPV/r, there is only one generic manufacturer producing a quality-assured stand-alone RTV 100mg tablet, with one additional product eligible for procurement (as it is Global Fund ERP reviewed). More competition is needed to help decrease the price, and at time of writing, WHO Prequalification was assessing two additional generic sources.⁸⁶

Stand-alone heat-stable RTV is particularly critical for additional boosting for people who are co-infected with tuberculosis (TB), and for boosting DRV as a part of a third-line regimen.

WHO Guidelines

RTV is recommended for second-line treatment as a protease inhibitor booster for adolescents, pregnant and breastfeeding women, adults and people who are co-infected with TB or hepatitis B virus (HBV).²²

RTV is recommended as a protease inhibitor booster for second-line treatment for children, including those who are co-infected with TB or HBV, and for first-line treatment for children below three years of age.²²

Paediatrics

RTV is approved for use in children from one month of age by the US FDA.

A liquid formulation is available. However, the solution has a bitter aftertaste and contains 43 % alcohol, making it ill-adapted for children. No generic liquid formulation has yet been prequalified.

There is an urgent need for a better adapted paediatric formulation of RTV. In April 2011, a meeting held by WHO on short-term priorities for antiretroviral drug optimisation called for heat-stable RTV formulations containing 25mg of RTV; both the originator and generic companies are yet to work on developing this tablet formulation. The Drugs for Neglected Diseases *initiative* (DNDi) is working on RTV heat-stable granules for children co-infected with TB who need additional boosting while on LPV/r treatment. The registration of this product is expected by 2015.²¹¹

Patents

Patent filing on RTV has increased dramatically since 1993 and now includes more than 800 patent families.²¹²

The basic patent on RTV could not be applied for in India as the country did not grant patents on medicines before the full implementation of the TRIPS agreement. Nevertheless, Abbott has filed a number of patent applications on the polymorph and solid pharmaceutical dosage (tablet) formulations of RTV.^{213, 214, 215, 216}

A pre-grant opposition on the RTV polymorph application was first filed in May 2007.²¹⁷ Abbott subsequently filed a series of additional divisional patent applications that contained matter from the previously filed RTV polymorph patent application.²¹⁸ Pre-grant oppositions were subsequently filed by generic manufacturers on the divisional applications. In 2011, the RTV polymorph patent application was rejected by the patent office²¹⁹ and the divisional applications were subsequently abandoned by Abbott.²²⁰ These oppositions have safeguarded Indian-produced generic supply for people in both India and

the developing world where patents are not enforced.

The only RTV patent application which remains is one that claims a solid pharmaceutical dosage (tablet) formulation, and is under examination; a group of people living with HIV/AIDS filed a pre-grant opposition in July 2012.²¹⁷

Patents related to polymorphic forms of RTV have also been filed in other middle-income countries. In China, a patent on crystalline polymorph was granted.³⁹ In Brazil, the patent application on crystalline polymorph was rejected.³⁹ RTV is produced locally, as the basic patent is being opposed by Brazilian generic manufacturers in the courts. In 2012, a Brazilian private laboratory, Cristália, won a bidding process to supply RTV 100mg soft-gel capsules.²²¹

In April 2010, Ecuador issued a compulsory licence, allowing Eskegroup – 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 expires in 2014.²²² The compulsory licence, Ecuador's first, followed a decree by the President in October 2009 declaring access to essential medicines to be in the public interest, and allowing the national intellectual property office to issue compulsory licences, based on Article 31 of the TRIPS agreement.²²³ According to the Ministry of Health, the compulsory licence has already yielded savings of US\$150,000.

In September 2012, the Indonesian government issued compulsory licences on several key ARVs including LPV/r. This licence will last until the end of patent period in August 2018.⁴²

TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION

- Therapeutic class: Nucleotide reverse transcriptase inhibitor (NtRTI).
- 2013 WHO Guidelines: TDF is recommended for first- and second-line treatment for children over three years of age, for adolescents and for adults.²²
- Originator company and product brand name: Gilead, Viread.
- First approved by US Food and Drug Administration (FDA): October 2001.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2012: US\$848 million 2011: \$738 million; 2010: \$732 million; 2009: \$667 million; 2008: \$621 million; 2007: \$613 million; 2006: \$689 million; 2005: \$778 million; 2004: \$783 million.^{122, 123, 124, 125, 126, 127, 128, 224, 225}
- Patents: The Academy of Sciences of the former Czechoslovakia applied for the basic patent on TDF in 1986, which has now expired in most countries.²³² Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997²³³ and to the fumarate salt of tenofovir disoproxil in 1998.²³⁴ These are due to expire in 2017 and 2018, respectively. TDF combination patents with emtricitabine (FTC) and rilpivirine (RIL) have also been granted in many countries, expiring in 2024.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

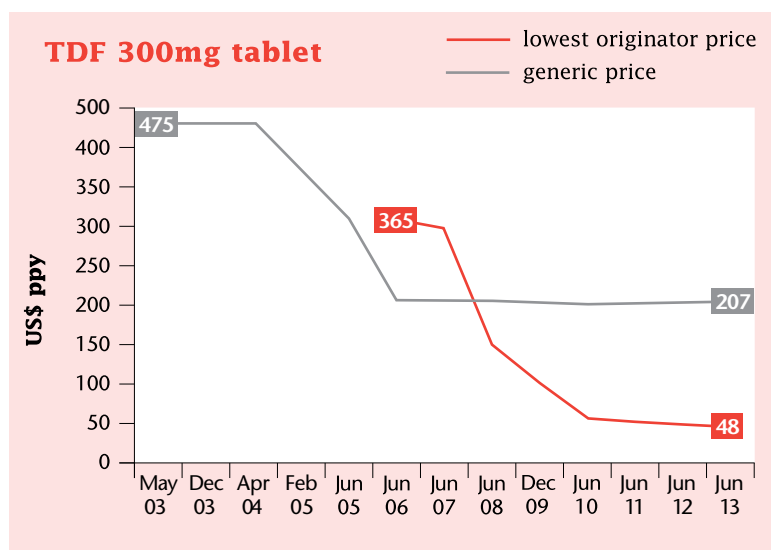
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Gilead		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
TDF 300mg tablet	1	207 (0.567)	365 (1.000)	55 (0.150)	61 (0.167)	48 (0.132)	49 (0.133)	55 (0.150)	57 (0.157)

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

As of May 2013, six generic sources of TDF 300mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2006, the generic price has decreased by 87%. The originator price has remained constant for low-income countries since 2006 (see Annex 2 for a list of these countries).



SPOTLIGHT ON ACCESS ISSUES

TDF is included in a number of fixed-dose combinations – please refer to those drug profiles for further information.

WHO guidelines

TDF is included in the 2013 WHO Guidelines as a part of first-line treatment for adolescents, pregnant and breast-feeding women, adults and people who are co-infected with tuberculosis (TB) or hepatitis B virus (HBV).

TDF is now recommended as the second preferred alternative NRTI for children between the ages of three and 12 years of age. In adolescents 12 years and older, TDF is the preferred first-line NRTI. If it was not used as a first-line component regimen, TDF can be used as a second-line treatment option for children, adults, adolescents and pregnant women.²²

Paediatrics

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

This approval is a step forward, as it opens up the possibility of aligning first-line ART regimens for adults and children over three years of age. This would simplify drug procurement for HIV programmes as the same medicines would be purchased for all.

Patents

The price of TDF fell dramatically between 2005 and 2010, due to generic production that started in India in 2005 and thanks to patent oppositions filed by civil society groups in 2006²²⁶ and 2007.²²⁷ In a major victory for access to medicines, the Indian patent office rejected several patent applications

in September 2009 relating to the pro-drug,²²⁸ the fumarate form,²²⁹ the intermediate,²³⁰ the combination of TDF with FTC²³¹ and the once-a-day pill TDF/FTC/EFV.²³² The patents were rejected on the grounds that they lack an inventive step and do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law.^{228, 229, 234}

Nevertheless, divisional applications have already been filed by Gilead for key applications covering the pro-drug²²⁸ – which has been rejected – and the fumarate salt,²³⁴ as well as the combinations of TDF with FTC, EFV and LPV/r.²³⁵ Three divisional applications on the key application covering the fumarate salt have been opposed by generic companies and civil society organisations; one has been withdrawn by Gilead, others are still pending.²²⁸

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.²³⁶ After the Brazilian government declared TDF as a medicine of public interest and the Brazilian patent office rejected the patent in September 2008, Gilead launched a legal challenge against the patent office's decision in January 2010, which is still pending. Gilead also requested a divisional patent, which was opposed by civil society groups²³⁷ and then rejected, in another victory for access to medicines, in May 2011.²³⁸

Even though patent oppositions by Indian and Brazilian civil society were still pending – and Gilead's monopoly in those countries therefore unsecured – the company signed voluntary licensing (VL) agreements in 2006 with key generic manufacturers in India and South Africa. One Indian generic

manufacturer, Cipla, chose not to 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 2006 VL, Gilead retained control over the manufacture and distribution of the active pharmaceutical ingredient (API) and the finished product. Importantly, a number of countries, including middle-income countries with substantial burdens of HIV, were excluded.²³⁹ Gilead and participating Indian manufacturers divided up developing country markets for TDF and TDF-based fixed-dose combinations, whereby the generic manufacturers could only export to a limited pre-defined list of 95 countries, against the payment of a 5% royalty.¹³⁵

In July 2011, Gilead signed a further licence agreement with the Medicines Patent Pool authorising the Pool to sub-licence to generic manufacturers a range of products: TDF, FTC and three new products currently under development – cobicistat (COBI), an investigational antiretroviral boosting agent; elvitegravir (EVG), an investigational integrase inhibitor; and a combination of these four products in a once-daily, single tablet regimen, known as the 'Quad' (TDF/FTC/COBI/EVG, marketed as Stribild).

Uniquely, the full terms of the licence have been made publically available.²⁴⁰ The licences are non-exclusive, non-transferable and non-sub-licensable. For TDF and combinations that include TDF, the royalty rate is 3%, which will increase to 5% if a patent is granted

Continued overleaf ❖❖❖

❖ *Tenofovir Disoproxil Fumarate (TDF) continued*

in India on a combination that includes TDF. Royalties are waived on formulations specifically designed for paediatric populations under 12 years old.

However, as with the 2006 licences, restrictions exist: only Indian generic companies are eligible for production. Geographic limitations on where the products can be sold are in place for all products, with the exception of paediatric products. For TDF, the list of eligible territories has increased from the 95 territories covered by the 2006 licences, to 112 territories. However, licenced manufacturers are still unable to supply countries such as China, Thailand, Argentina, Peru, Egypt or Ukraine, leaving people living with HIV in these countries unable to benefit from competitive prices under the licence. The licence with the Pool also retains the restrictions in the 2006 licence on the manufacture and supply of APIs.

Through these licences, Gilead is seeking to control the market, even though in many countries patents are not in place. Interestingly, out of the 112 territories, patents are only granted in ARIPO countries on TDF combinations with FTC and RIL. The TDF patent status in OAPI countries is not known; combination patents are also filed in India and Indonesia.

Countries that are excluded from the licences, and which have no patents on TDF, can either choose to produce locally – provided they have sufficient manufacturing capacity and can identify and access an alternative source of API – or to source TDF from the two Indian generic manufacturers that are not Gilead sub-licencees. Countries that are excluded from the licences but which have, or will have, patents on

TDF will have to rely on the use of compulsory licences. In that respect the Pool licence is unique, in that it explicitly allows a licencee to supply an excluded country if it has granted a compulsory licence, regardless of the geographic limitations specified in the licence.

Having signed the 2006 licence, Aurobindo and MedChem subsequently signed the 2011 licence and used a clause in the latter to terminate the former.²⁴¹ This feature of the Gilead-Patent Pool licence, known as ‘unbundling’, allows generic companies to terminate the TDF component of the 2006 licence when signing licences for the remaining products. Aurobindo and MedChem terminated their previous TDF licence with Gilead, whilst licensing EVG, COBI and the Quad.

Other generic companies that signed the 2006 VL are unlikely to follow suit, as they also signed voluntary licences with Gilead, outside of the Pool, on the same products in July 2011. On the same day the Pool licences were made public, Gilead also announced it had signed separate, bilateral, licensing agreements with four ‘preferred’ Indian generic manufacturers.²⁴² The licences cover TDF and FTC, as well as providing semi-exclusive rights for five years to market EVG, COBI and the Quad to defined territories, including nine countries excluded from the Gilead-Patent Pool licence. The terms of this agreement have not been made public but based on information from Gilead, these licences contain no termination clause (if a patent is revoked, there is no option to terminate the VL), nor a term on compulsory licences (if a CL is issued in an excluded

country, the licencee cannot make use of it). For details of voluntary licences see Annex 3.

Brazil, one of the countries excluded from both the 2006 and the 2011 licences, today pays \$715 ppy for TDF,⁵⁵ following negotiations with Gilead. This price is substantially higher than the lowest WHO-prequalified generic price available. In February 2011, the Brazilian government announced the beginning of local production of TDF through a partnership.²⁴³

This deal is particularly significant, as the access challenges Brazil experiences today, will be faced by other developing countries in coming years. Brazil’s actions to improve the accessibility and affordability of TDF⁵⁵ and other newer medicines will have wider implications for all developing countries, as price reductions achieved by Brazil will set a target price for other middle- and lower middle-income countries. The size of Brazil’s cohort is also critical; with approximately 64,000 people taking TDF,⁵⁵ the country could stimulate an international generic market where prices are reduced through competition and economies of scale.

Gilead and BMS have applied for patents on fixed-dose combinations of TDF/FTC, TDF/FTC/EFV and TDF/FTC/RIL which will not expire before 2024 and 2026 respectively, where granted.^{244, 245}

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including TDF and its combination with FTC and EFV. This licence will last until the end of the patent period in November 2024.⁴²



ZIDOVUDINE (AZT or ZDV)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2013 WHO Guidelines: AZT is recommended for first- and second-line treatment for infants, children, adolescents and adults.²²
- Originator company and product brand name: GlaxoSmithKline (GSK), Retrovir. 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 approved by US Food and Drug Administration (FDA): March 1987.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25}
- World sales of originator product: 2005: US\$84 million; 2004: \$80 million. After 2005, sales are not reported in the company's annual report.^{28, 29}
- Patents: Glaxo Wellcome filed patents on AZT in 1985.²⁴⁶ 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 unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy
AZT 10mg/ml oral solution (paediatrics)	24 ml	399 (0.046)	91 (0.010)	78 (0.009)	100 (0.011)			
AZT 60mg tablet (paediatrics)	4			96 (0.066)		43 (0.029)		
AZT 100mg capsule (paediatrics)	xx	(0.102)	(0.046)	(0.050)				
AZT 250mg capsule (paediatrics)	xx	(0.159)						
AZT 300mg tablet	2		73 (0.100)	79 (0.108)	79 (0.108)	70 (0.096)	85 (0.117)	71 (0.097)

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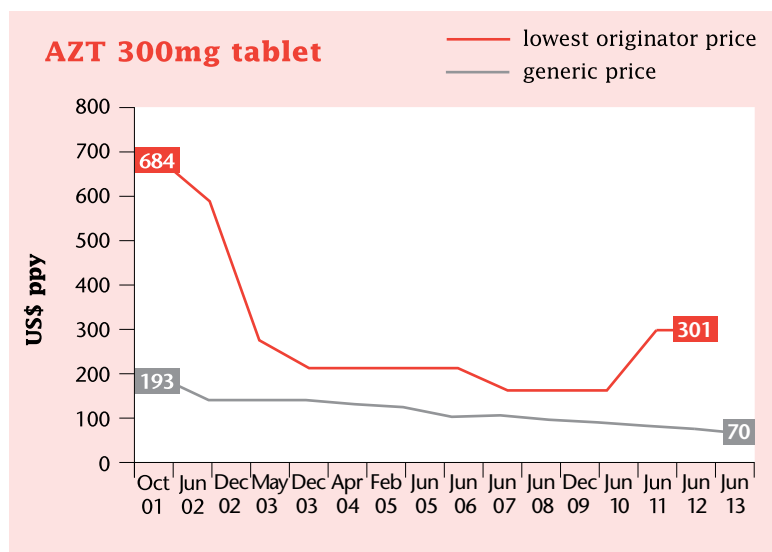
❖ Zidovudine (AZT or ZDV) continued

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

As of May 2013, a number of generic sources of AZT 300mg tablet are quality-assured by US FDA or WHO prequalification, and six gave a price for this report. The lowest price is shown here.

The originator company has not provided pricing information since 2011 for the 300mg tablet, and discontinued production in 2012.

Since 2001, the generic price has decreased by 64%.



SPOTLIGHT ON ACCESS ISSUES

Since 2012, ViiV has ceased production of 300mg AZT tablets. Production of other doses (100mg and 250mg capsules) and AZT-based fixed-dose combinations will continue.

AZT is included in a number of fixed-dose combinations – please refer to those drug profiles for further information. AZT single-drug formulations continue to have a role in prevention of mother-to-child programmes (PMTCT) programmes in developing countries.

WHO Guidelines

AZT is recommended for first- and second-line treatment, for infants, children, adolescents and adults.²²

For adults, adolescents and pregnant women, AZT is one of the recommended alternative first-line treatments.

AZT is recommended for children younger than three years of age as one of the NRTIs, and is a component of alternative first-line treatment for children between three and 12 years of age. If it was not used as a first-line component regimen, it can be used as a second-line treatment option for infants and children.

Paediatrics

AZT is approved for use and is widely used in children. Toxicity risks are associated with AZT, with possible anaemia developing over the first few months of therapy, however the drug remains much better tolerated than stavudine (d4T).²²

There are at least two WHO-prequalified generic sources of AZT 10mg/ml oral solution and 100mg capsule, and at time of writing,

WHO Prequalification was assessing an additional generic source of AZT 60mg tablet.⁸⁶

Patents

AZT was first discovered in 1964 as an anti-cancer medicine. The US 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 HIV and brought the drug onto the market in 1987 as one of the most expensive ever sold.

Patents have by now expired in most countries and the risk of facing a patent related access barrier is quite low though some formulation patents are still enforced in many countries.



ABACAVIR/ LAMIVUDINE (ABC/3TC)

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) in a double fixed-dose combination.
- 2013 WHO Guidelines: ABC/3TC is recommended as one of two preferred first-line NRTI backbones for children less than three years of age, and as the preferred NRTI backbone of a regimen for children between three and 12 years of age. For adolescents older than 12 years of age and adults, ABC/3TC can be considered in special circumstances as an NRTI backbone treatment option.²²
- Originator company and product brand name: GlaxoSmithKline (GSK), Kivexa (Europe), Epzicom (US). 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 approved by US Food and Drug Administration (FDA): August 2004.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.
- World sales of originator product: 2012: US\$1 billion; 2011: \$994 million; 2010: \$899 million; 2009: \$834 million; 2008: \$721 million; 2007: \$641 million; 2006: \$475 million; 2005: \$233 million.
26, 27, 28, 29, 30, 141, 142, 143
- Patents: Most patents on ABC or 3TC also affect this combination. In addition, GSK applied for patents specifically related to the combination,²⁴⁸ which are due to expire in 2016 in the US and in 2019 in Europe.²⁷

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

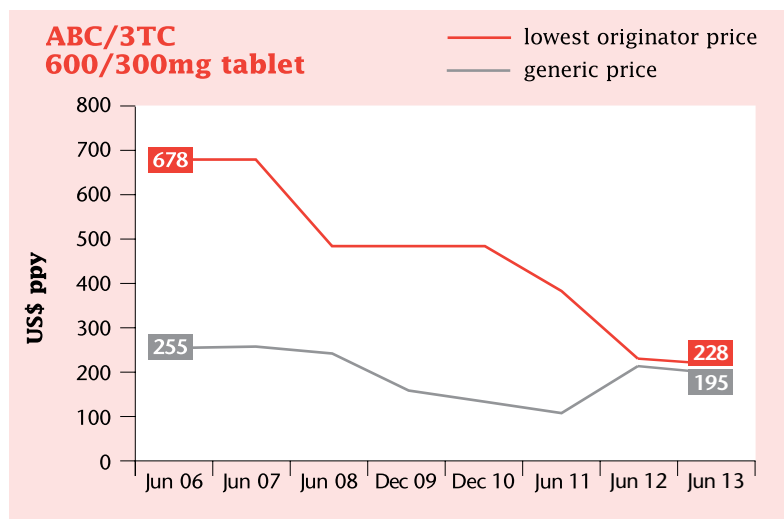
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aurobindo	Cipla	Mylan
ABC/3TC 60/30mg tablet (paediatrics)	4		229 (0.157)	170 (0.117)	128 (0.088)
ABC/3TC 600/300mg tablet	1	228 (0.624)	219 (0.600)	219 (0.600)	195 (0.533)

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

As of May 2013, three generic sources of ABC/3TC 600/300mg tablets are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2012, the generic price has decreased by 8.5%, although it remains higher than in previous years. Since 2006, the originator price has decreased by 66%. This price is only available for low-income countries, least-developed countries and sub-Saharan Africa.



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SPOTLIGHT ON ACCESS ISSUES

Price remains an issue with the ABC/3TC 600/300mg fixed-dose combination. The current lowest generic price is still more than double the lowest WHO-prequalified generic price for the AZT/3TC 300/150mg tablet.

WHO Guidelines

ABC/3TC is one of two preferred first-line NRTI backbones (the other being AZT/3TC) for infants and children younger than three years of age, together with LPV/r (the preferred option) or with NVP (the alternative option).

For children between three and 12 years of age, ABC/3TC is the preferred NRTI backbone. For adolescents 12 years

of age and older ABC/3TC can be considered in special circumstances as a treatment option.²²

Paediatrics

For paediatrics too, the price of ABC/3TC 60/30mg tablet remains an issue, as the lowest prequalified generic price is still more than double the lowest price for AZT/3TC 60/30mg tablet.

Patents

GlaxoSmithKline (GSK) could not apply for basic patents related to ABC or 3TC in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement. This allowed Indian drug manufacturers to develop

generic versions of each medicine and of a combination of the two.

However, GSK widely applied for patents in other developing countries where possible. GSK hold patents on fixed-dose combinations of ABC with 3TC or with FTC (and with AZT) in China, Russia, ARIPO and OAPI countries, and elsewhere.³⁹

In November 2012, Ecuador issued a compulsory licence on ABC/3TC. The licence was issued to Ecuadorean manufacturer Acroxmax, in a bid to reduce the cost by 75%.¹⁴⁷

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



STAVUDINE / LAMIVUDINE (d4T/3TC)

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) in a double fixed-dose combination.
- 2013 WHO Guidelines: d4T/3TC is an alternative NRTI backbone of first-line treatment for HIV-infected infants and children below three years of age. For children above three years of age and adolescents, d4T/3TC can be used as a NRTI backbone in special circumstances. Use of d4T as a first-line treatment should be discontinued, except in special cases where other ARVs cannot be given.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on both d4T and 3TC meant that generic companies were able to produce this fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25} The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.
- World sales of originator product: not applicable.
- Patents: Individual patents on d4T or 3TC 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 unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

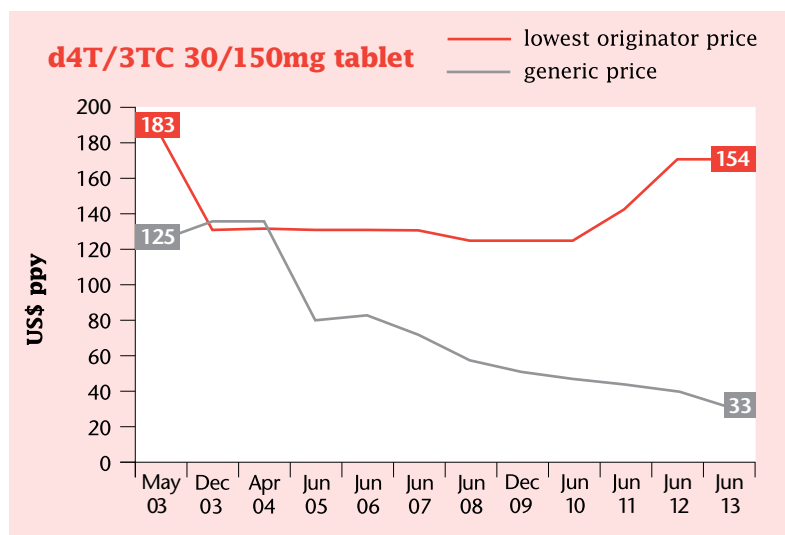
	Daily dose	Cipla	Hetero	Mylan	Ranbaxy	Strides
d4T/3TC 6/30mg dispersible tablet (paediatrics)	4	46 (0.032)				
d4T/3TC 12/60mg dispersible tablet (paediatrics)	2	40 (0.055)				
d4T/3TC 30/150mg tablet	2	41 (0.056)	39 (0.053)	43 (0.058)	33 (0.046)	36 (0.049)

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

As of May 2013, five generic sources of d4T/3TC 30/150mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

As there is no originator fixed-dose combination, the price shown for the originator product is the sum of the two individual originator products. The price for the originator product stops at 2012, as pricing information on stavudine as a single product is no longer included in Untangling the Web.

Since 2003, the generic price has dropped by 74%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF, a number of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens because of funding concerns.

WHO Guidelines

WHO has advised countries to phase out d4T-based regimens and discontinue d4T use in first-line treatment because of long-term irreversible side effects, except in cases where other ARVs cannot be used.²² Instead, AZT- or TDF-based first-line regimens should be used, together with either 3TC or FTC and

either EFV or NVP.²² d4T as a first-line treatment for children should be discontinued, except in cases where other ARVs cannot be used or are not available.²² For infants and children younger than three years of age, d4T/3TC is an alternative NRTI in first-line treatment. For children above three years of age and for adolescents, d4T/3TC can be used as an NRTI treatment in special circumstances.

Paediatrics

There is currently only one WHO-prequalified generic manufacturer of paediatric formulations, for both 6/30mg and for 12/60mg tablets.

Patents

Generic companies in certain developing countries were able to develop this fixed-dose combination because either there were no patents or patents were not enforced.

d4T/3TC may not be available in countries where patents on new formulations of 3TC are granted and enforced, however. These will not expire before 2018.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



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

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a triple fixed-dose combination.
- 2013 WHO Guidelines: d4T/3TC/NVP can be used in special circumstances for first-line treatment for HIV-infected infants and children less than three years old, where AZT and ABC are contraindicated. For children above three years of age and adolescents, d4T/3TC/NVP can be used as an option under special circumstances. Use of d4T as a first-line treatment should be discontinued, except in special cases where other ARVs cannot be given.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on d4T, 3TC and NVP meant that generic companies were able to produce this fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25} The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.^{32, 33}
- World sales of originator product: not applicable.
- Patents: Individual patents on d4T, 3TC or NVP also affect this combination. Cipla applied for patents specifically related to the combination in several African countries.²⁴⁹

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

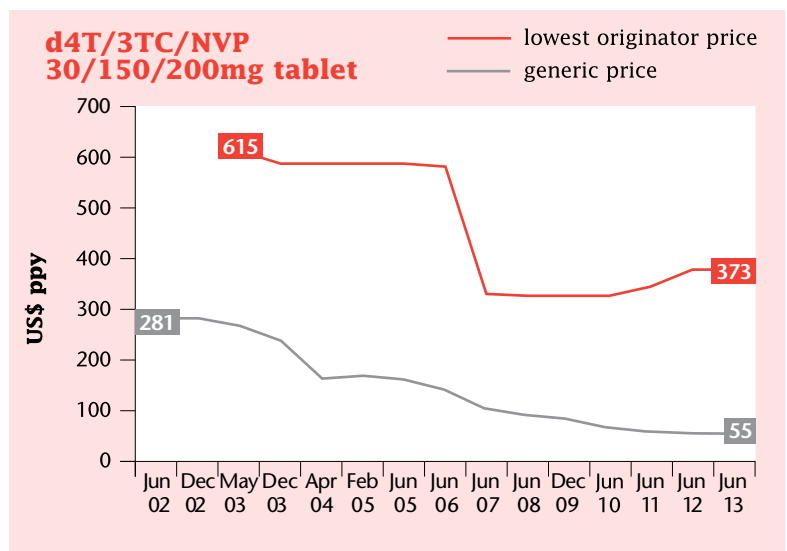
	Daily dose	Cipla	Hetero	Mylan	Ranbaxy	Strides
d4T/3TC/NVP 6/30/50mg dispersible tablet (paediatrics)	4	56 (0.038)				
d4T/3TC/NVP 12/60/100mg dispersible tablet (paediatrics)	2	52 (0.072)				
d4T/3TC/NVP 30/150/200mg tablet	2	55 (0.075)	59 (0.081)	64 (0.088)	62 (0.085)	58 (0.079)

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

As of May 2013, five generic sources of d4T/3TC/NVP 30/150/200mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

As there is no originator fixed-dose combination, the price shown for the originator product is the sum of the three individual originator products. The price for the originator product stops at 2012, as pricing information on stavudine as a single product is no longer included in Untangling the Web.

Since 2002, the generic price has dropped by 80%.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF, a number of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens because of funding concerns.

WHO Guidelines

WHO has advised countries to phase out d4T-based regimens and discontinue d4T use in first-line treatment because of long-term irreversible side effects, except in cases where other ARVs cannot be used.²² Instead, AZT or TDF-based first-line regimens should be used,

together with either 3TC or FTC and either EFV or NVP.²²

For infants and children up to adolescents, d4T/3TC/NVP can be used in cases where other ARVs cannot be used.

Paediatrics

There is only one WHO-prequalified generic manufacturer for both the 30/6/50mg and the 60/12/100mg tablets.

Patents

As none of the individual components were patented in India, Cipla

was first able to develop this combination in 2000.²⁵⁰ Many generic manufacturers have followed suit in other developing countries where the medicines were not patented, such as in Thailand. Extensive competition from numerous generic manufacturers has made this combination the most affordable triple ARV combination treatment to date.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE (TDF/FTC)

GENERAL INFORMATION

- Therapeutic class: One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a double fixed-dose combination.
- 2013 WHO Guidelines: TDF/FTC is recommended for first-line treatment for adults, pregnant and breast-feeding women, adolescents and people co-infected with tuberculosis (TB) or hepatitis B (HBV). For adolescents above the age of 12, TDF/FTC is the preferred first-line NRTI backbone.²²
- Originator company and product brand name: Gilead, Truvada.
- First approved by US Food and Drug Administration (FDA): August 2004.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults but not in the 4th edition for children. 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.²⁴
- World sales of originator product: 2012: US\$3.2 billion; 2011: \$2.9 billion; 2010: \$2.7 billion; 2009: \$2.5 billion; 2008: \$2.1 billion; 2007: \$1.6 billion; 2006: \$1.2 billion; 2005: \$568 million; 2004: \$68 million.^{122, 123, 124, 125, 128}
- Patents: Most patents related to TDF or to FTC also affect this combination. Gilead applied for patents specifically related to this combination in 2004, which are due to expire in 2024.²⁵¹

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

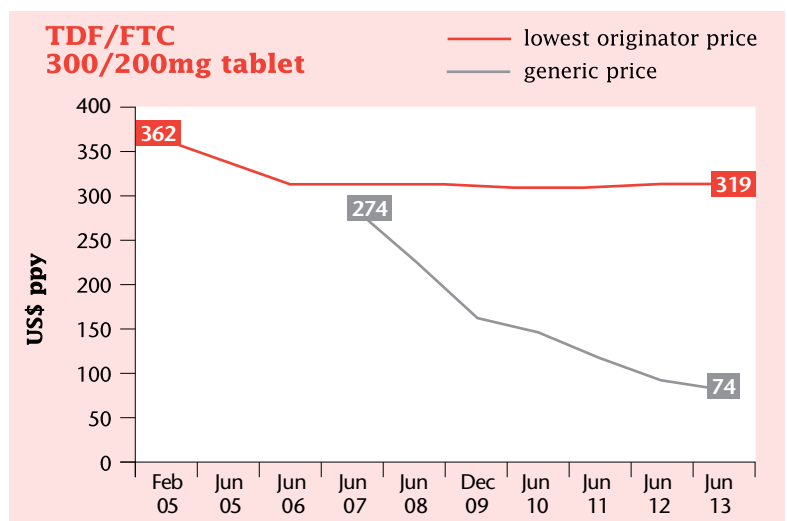
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Gilead		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy
		Category 1 countries	Category 2 countries					
TDF/FTC 300/200mg tablet	1	319 (0.875)	548 (1.500)	74 (0.203)	110 (0.300)	79 (0.217)	74 (0.203)	110 (0.300)

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

As of May 2013, four generic sources of TDF/FTC 300/200mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

The originator price decreased by almost 12% since 2005, and the generic price by almost 73% since 2007.



Continued overleaf ❖❖❖

SPOTLIGHT ON ACCESS ISSUES

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²² This formulation is therefore interchangeable with TDF/3TC.

WHO Guidelines

TDF/FTC is recommended for first-line ART for adolescents, pregnant and breast-feeding women, adults and people co-infected with tuberculosis (TB) or HBV. In adolescents 12 years and older, TDF/FTC is the preferred first-line NRTI in an ART regimen. If it was not used as in a first-line regimen, it can be used as a second-line treatment option, together with a protease inhibitor, for adolescents, pregnant and breastfeeding women, and adults.²²

WHO recommends TDF/3TC for children between three and 12 years of age as an alternative NRTI. If an AZT- or d4T-based

regimen was used as first-line treatment, TDF/FTC can be used as a component of second-line treatment for children.²²

Paediatrics

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

This approval is a step forward, as it opens up the possibility of aligning first-line ART regimens for adults and children over three years of age. This would simplify drug procurement for HIV programmes as the same medicines would be purchased for all.

Patents

Patents on TDF/FTC exist in Brazil, China and in ARIPO countries.³⁹

TDF/FTC is produced by Indian generic companies under voluntary licence from Gilead. However, Cipla – which does not have a voluntary

licence – is able to produce TDF/FTC because neither of the individual components is patented in India. Gilead has applied for a divisional patent related to this combination in India which, if granted, will affect production by Cipla.²⁵²

In September 2012, the Indonesian government issued compulsory licences on several key ARVs including on TDF/FTC. This licence will last until the end of patent period in November 2024.⁴²

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination. For full details on the patent status of TDF in India and Brazil, including the voluntary licence agreements signed by Gilead with generic companies and with the Medicines Patent Pool (which also cover this combination), as well as the Brazilian initiative for local production, please also refer to Annex 3.



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

GENERAL INFORMATION

- Therapeutic class: One nucleotide reverse transcriptase inhibitor (NtRTI), one nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a triple fixed-dose combination.
- 2013 WHO Guidelines: TDF/FTC/EFV is recommended for first-line treatment for adults, pregnant and breast-feeding women, adolescents and people co-infected with tuberculosis (TB) or hepatitis B (HBV).²²
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb (BMS)/Merck, Atripla.
- First approved by US Food and Drug Administration (FDA): July 2006.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults. EFV is also included as a stand-alone product in the 4th edition for children. 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.²⁵⁴
- World sales of the originator: 2012: US\$3.6 billion; 2011: \$3.2 billion; 2010: \$2.9 billion; 2009: \$2.4 billion; 2008: \$1.6 billion; 2007: \$903 million; 2006: \$164 million.^{122, 123, 124, 128}
- Patents: Most patents related to TDF, FTC, TDF/FTC or to EFV also affect this combination. Gilead and BMS jointly applied for patents specifically related to this combination in 2006,²⁴⁵ which are due to expire in 2026.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

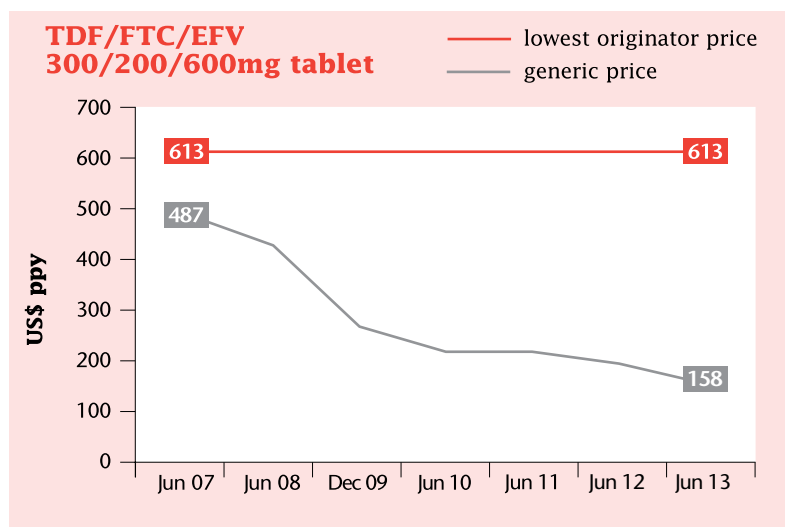
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Merck		Aspen	Aurobindo	Cipla	Hetero	Mylan	Ranbaxy
		Category 1 countries	Category 2 countries						
TDF/FTC/EFV 300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	139 (0.381)	170 (0.467)	158 (0.433)	137 (0.375)	161 (0.442)	164 (0.450)

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

As of May 2013, two generic sources of TDF/FTC/EFV 300/200/600mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2007, the originator price has remained the same, whereas the generic price has decreased by almost 68%.



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.

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²² This formulation is therefore interchangeable with TDF/3TC/EFV.

There are currently three quality-approved generic sources of TDF/FTC/EFV. The lowest WHO-prequalified generic price for this product is \$158 ppy, which is still higher than the lowest reported price for TDF/3TC/EFV at \$139 ppy.

At time of writing, WHO Prequalification was assessing four additional generic sources of TDF/FTC/EFV.⁸⁶

WHO Guidelines

TDF/FTC/EFV is recommended for first-line treatment for adolescents, pregnant and breast-feeding women, adults and people co-infected with tuberculosis (TB) or HBV. In adolescents, TDF/FTC/EFV is the preferred first-line treatment.²²

WHO guidelines recommend EFV-based regimens as the preferred first-line treatment options for pregnant women, regardless of trimester stage, and women of reproductive age.²² WHO advice also states the programmatic consequences of avoiding EFV use in pregnancy and supports its use as part of a simplified first-line treatment.²²

In children between three and 12 years of age, TDF/FTC/EFV is the second preferred alternative NRTI for first-

line treatment. It can also be used as a second-line treatment option in children three years of age and older, if AZT or d4T, in combination with LPV/r, were used in first-line treatment.

Paediatrics

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

This approval is a step forward, as it opens up the possibility of aligning first-line ART regimens for adults and children over three years of age. This would simplify drug procurement for HIV programmes as the same medicines would be purchased for all.

Patents

The originator version of TDF/FTC/EFV (marketed as 'Atripla') became the first multi-class antiretroviral drug approved by the US FDA in July 2006. As Gilead's TDF and FTC are combined with Bristol-Myers Squibb's EFV, Atripla also marked the first collaboration between two US pharmaceutical companies combining patented HIV medicines into one product.²⁵⁵ Atripla is jointly marketed in North America and Europe by Gilead and BMS, but marketing and distribution in much of the developing world is handled by Merck.²⁵¹

As none of the individual components are currently patented in India, this combination is produced by several Indian generic companies. However, patent applications may threaten this production. Gilead filed a patent application related to TDF/FTC/EFV,^{245, 256} which was rejected by the patent

office,²⁵⁷ as combinations of known medicines are not patentable under India's patent law. Gilead has filed several divisional applications – one of which is still pending examination.²⁵⁸

In addition, BMS and Gilead have together filed for a patent for TDF/FTC/EFV^{255, 259} which, if granted, could impact access to improved first-line ART in the developing world. In 2010, Cipla filed a pre-grant opposition to this patent application, which is under examination in India.

Gilead has signed a number of voluntary licence deals with Indian manufacturers on TDF and TDF-based combinations.

Given their limited geographic scope however, countries not covered under these licences may face barriers in procuring TDF/FTC/EFV from Indian manufacturers producing this combination outside of the voluntary licence agreements.

In September 2012, the Indonesian government issued compulsory licences on several key ARVs including on TDF/FTC/EFV. This licence will last until the end of patent period in November 2024.⁴²

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination. For full details on the patent status of TDF in India and Brazil, including the voluntary licence agreements signed by Gilead with generic companies and with the Medicines Patent Pool (which also cover this combination), as well as the Brazilian initiative for local production, please also refer to Annex 3.



TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

GENERAL INFORMATION

- Therapeutic class: One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a double fixed-dose combination.
- 2013 WHO Guidelines: TDF/3TC is recommended for first-line treatment for adults, pregnant and breast-feeding women, adolescents and people co-infected with tuberculosis (TB) or hepatitis B (HBV). In adolescents above the age of 12, TDF/3TC is the preferred first-line NRTI backbone.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on both TDF and 3TC meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults. 3TC is also included as a stand-alone product in the 4th edition for children.^{24, 25}
- 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.²⁵⁴
- World sales of originator product: not applicable.
- Patents: Patents related to TDF or to 3TC also affect this combination. Cipla applied for patents specifically related to the combination in several African countries, and other patent applications may exist.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

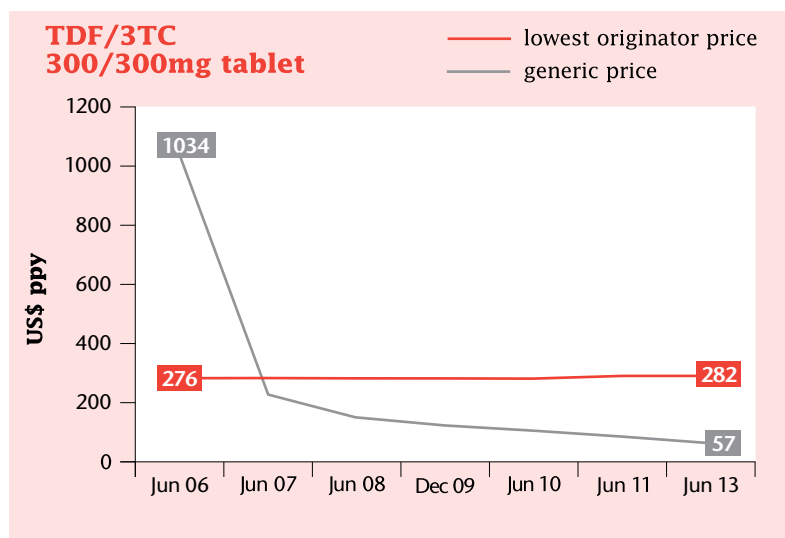
	Daily dose	Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy
TDF/3TC 300/300mg tablet	1	57 (0.157)	85 (0.233)	64 (0.177)	63 (0.173)	103 (0.281)	69 (0.188)

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

As of May 2013, five generic sources of TDF/3TC 300/300mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

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

Since 2006, the generic price has decreased by 94%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²² This formulation is therefore interchangeable with TDF/FTC.

The lowest priced WHO-prequalified generic source, at \$57 ppy, is substantially more affordable than the lowest priced WHO-prequalified generic source of TDF/FTC at \$74 ppy.

WHO Guidelines

TDF/3TC is recommended for first-line ART regimen for adolescents, pregnant and breast-feeding women, adults and people co-infected with tuberculosis (TB) or HBV. In adolescents over 12 years of age, TDF/3TC is the preferred first-line NRTI. If TDF/3TC was not used as a first-line component regimen, it can be used as a second-line treatment option, together with a protease inhibitor.²²

In children between three and 12 years of age, TDF/3TC is an alternative NRTI option. If AZT or d4T was used in first-line treatment, TDF/3TC can be used as a component of second-line treatment.²²

Paediatrics

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets. This approval is a step forward, as it opens up the possibility of aligning first-line ART regimens for adults and children over three years of age. This would simplify drug procurement for HIV programmes as the same medicines would be purchased for all.

The WHO Paediatric Antiretroviral Working Group 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.²²

Patents

There is no originator TDF/3TC fixed-dose combination. As neither of the individual components is currently patented in India, this combination is produced by several Indian generic companies.

However, Gilead has applied for patents in India related to TDF and 3TC which, if granted, may affect the production of not only TDF but also of this combination.

Gilead's voluntary licence on TDF is also used by some Indian generic companies to manufacture this combination. However, Gilead has applied for patents related to TDF in India which, if granted, will affect the production of not only TDF, but also of this combination.

In October 2012, the Brazilian government announced the introduction of two new fixed-dose combinations: TDF/3TC (300/300mg) and TDF/3TC/EFV (300/300/600mg).²⁵³ These combinations, which will be jointly supplied by Brazilian public laboratories Farmanguinhos, Funed and Lafepe, are expected to be available in 2013, although they are currently not registered with national regulatory agency ANVISA.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination. For full details on the patent status of TDF in India and Brazil, including the voluntary licence agreements signed by Gilead with generic companies and with the Medicines Patent Pool (which also cover this combination), as well as the Brazilian initiative for local production, please also refer to Annex 3.



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

GENERAL INFORMATION

- Therapeutic class: One nucleotide reverse transcriptase inhibitor (NtRTI), one nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a triple fixed-dose combination.
- 2013 WHO Guidelines: TDF/3TC/EFV is recommended for first-line ART regimen for adults, pregnant and breast-feeding women, adolescents and people co-infected with tuberculosis (TB) or hepatitis B (HBV).²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on TDF, 3TC and EFV meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults. 3TC and EFV are also included as stand-alone products in the 4th edition for children. 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.²⁵⁴
- World sales of originator product: not applicable.
- Patents: Patents related to TDF, 3TC and to EFV also affect this combination. Other patents specifically related to the fixed-dose combination may have been applied for.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

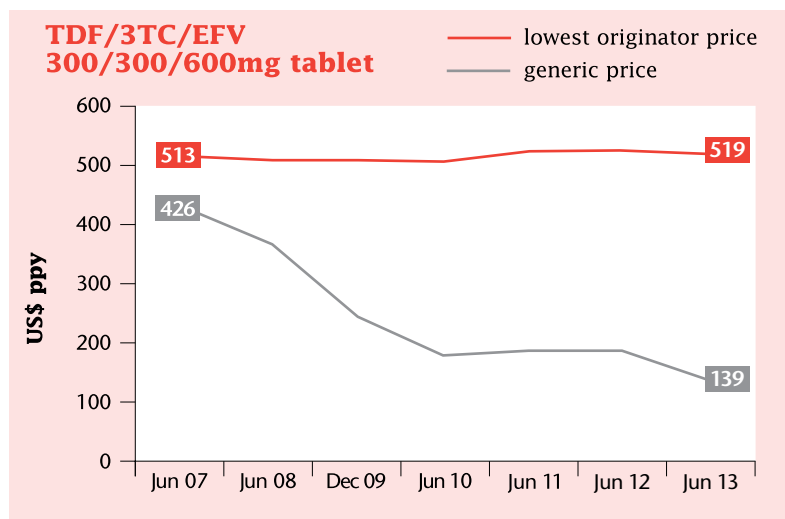
	Daily dose	Aurobindo	Cipla	Hetero	Mylan
TDF/3TC/EFV 300/300/600mg tablet	1	152 (0.417)	134 (0.367)	139 (0.382)	149 (0.408)

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

As of May 2013, two generic sources of TDF/3TC/EFV 300/300/600mg tablet are quality-assured by US FDA or WHO prequalification. 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 2007, the generic price has decreased by 67%. The combined price of the three individual originator products has increased by 1%.



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.

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.²² This formulation is therefore interchangeable with TDF/FTC/EFV.

The lowest priced WHO-prequalified source of TDF/3TC/EFV, at \$139 ppy, is more affordable than the lowest priced WHO-prequalified generic TDF/FTC/EFV at \$158 ppy.

At time of writing, WHO Prequalification was assessing an additional generic source of TDF/3TC/EFV.

WHO Guidelines

TDF/3TC/EFV is recommended for first-line treatment for adolescents, pregnant and breast-feeding women, adults and people co-infected with tuberculosis (TB) or HBV. In adolescents, TDF/3TC/EFV is the preferred first-line NRTI.

WHO guidelines recommend EFV-based regimens as the preferred first-line treatment options for pregnant women, regardless of trimester stage, and women of reproductive age.²² WHO advice also states the

programmatic consequences of avoiding EFV use in pregnancy and supports its use as part of a simplified first-line treatment.

In children between three and 12 years of age, TDF/3TC/EFV is the second preferred alternative NRTI of first-line treatment. It can also be used as a second-line treatment option in children three years of age and older if AZT or d4T, in combination with LPV/r, was used in first-line treatment.²²

Paediatrics

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

This approval is a step forward, as it opens up the possibility of aligning first-line ART regimens for adults and children over three years of age. This would simplify drug procurement for HIV programmes as the same medicines would be purchased for all.

Patents

There is no originator TDF/3TC/EFV fixed-dose combination. As none of the individual components are currently patented in India, this combination is produced by several Indian generic companies.

Gilead's voluntary licence on TDF is also used by some Indian generic companies to manufacture this combination. However, Gilead has applied for patents related to TDF in India which, if granted, will affect the production of not only TDF but also of this combination.

In October 2012, the Brazilian government announced the introduction of two new fixed-dose combinations: TDF/3TC (300/300mg) and TDF/3TC/EFV (300/300/600mg).²⁵³ These combinations, which will be jointly supplied by Brazilian public laboratories Farmanguinhos, Funed and Lafepe, are expected to be available in 2013, although they are currently not registered with national regulatory agency ANVISA.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination. For full details on the patent status of TDF in India and Brazil, including the voluntary licence agreements signed by Gilead with generic companies and with the Medicines Patent Pool (which also cover this combination), as well as the Brazilian initiative for local production, please also refer to Annex 3.



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

GENERAL INFORMATION

- Therapeutic class: One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a double fixed-dose combination, with one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a co-pack.
- 2013 WHO Guidelines: TDF/3TC + NVP is recommended for first-line treatment for children, adolescents, adults, and pregnant and breast-feeding women.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on TDF, 3TC and NVP meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Not included. TDF, 3TC and NVP are included as stand-alone products in the 18th edition for adults. 3TC and NVP are also included as stand-alone products in the 4th edition for children. 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.²⁵⁴
- World sales of originator product: not applicable.
- Patents: Patents related to TDF, 3TC and to 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 unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Hetero	Mylan
TDF/3TC + NVP 300/300 + 200mg tablets (co-pack)	1 kit (3 tablets)	122 (0.333)	113 (0.308)

SPOTLIGHT ON ACCESS ISSUES

This product is a co-pack and comes with a higher pill burden than existing fixed-dose combinations, such as TDF/3TC/EFV or TDF/FTC/EFV. This factor, along with emerging evidence around the safety of EFV in pregnant women, makes it a less preferred option.

At time of writing, WHO Prequalification was assessing an alternative generic source of TDF/3TC + NVP co-pack.⁸⁶

WHO Guidelines

Recommended as an alternative regimen for first-line ART for

adolescents, pregnant and breast-feeding women, adults and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV), where TDF/3TC/EFV-based combinations are contraindicated or not available.

In children between three and 12 years of age, TDF/3TC + NVP is the third preferred alternative NRTI. In adolescents 12 years of age and older, TDF/3TC + NVP is the second preferred alternative NRTI in a treatment regimen.²²

WHO guidelines recommend EFV-based regimens as the preferred

first-line treatment options for pregnant women, regardless of trimester stage, and women of reproductive age. WHO advice also states the programmatic consequences of avoiding EFV use in pregnancy and supports its use as part of a simplified first-line treatment.

Paediatrics

There is no paediatric fixed-dose combination of this product available.

Patents

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



ZIDOVUDINE/ LAMIVUDINE (AZT/3TC)

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) in a double fixed-dose combination.
- 2013 WHO Guidelines: AZT/3TC is recommended for first- and second-line treatment for infants, children, adolescents and adults.²²
- 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 approved by US Food and Drug Administration (FDA): September 1997.²³
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children. 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.
- World sales of the originator: 2012: US\$270 million; 2011: \$521 million; 2010: \$588 million; 2009: \$649 million; 2008: \$713 million; 2007: \$888 million; 2006: \$1 billion; 2005: \$1.1 billion; 2004: \$1.1 billion.^{26, 27, 28, 29, 30, 31, 141, 142, 143}
- Patents: Patents related to AZT and to 3TC also affect this combination. GSK applied for patents specifically related to the use of AZT and 3TC in combination,²⁶¹ and to the tablet formulation of the fixed-dose combination,²⁶² which were due to expire in 2012 and 2017, respectively. However, a patent on AZT/3TC tablet formulation expiring in 2017 has been officially withdrawn.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

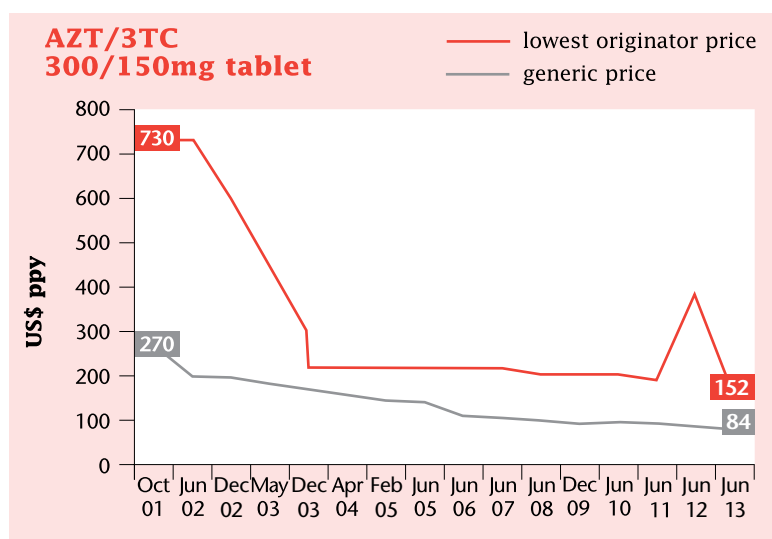
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Universal Corporation
AZT/3TC 60/30mg tablet (paediatrics)	4		56 (0.038)	73 (0.050)			55 (0.038)		73 (0.050)	
AZT/3TC 300/150mg tablet	2	152 (0.208)	84 (0.115)	91 (0.125)	93 (0.128)	88 (0.121)	85 (0.117)	125 (0.171)	84 (0.115)	92 (0.127)

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

As of May 2013, eight generic sources of AZT/3TC 300/150mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 79% while the generic price has dropped by 69%. Since last year's edition of Untangling the Web, the originator price has dropped by 61%, although this price is reserved for low-income countries, least-developed countries and sub-Saharan Africa.



SPOTLIGHT ON ACCESS ISSUES

AZT/3TC 300/150mg formulations continue to have a role in prevention of mother-to-child transmission programmes in developing countries.

WHO Guidelines

AZT is recommended for adults, adolescents and pregnant women as one of the alternative first-line treatments. If it was not used as a first-line component, it can be used as a component of second-line treatment for infants, children, adults, adolescents, pregnant and breast-feeding women.²²

TDF-based regimens are recommended over AZT-based regimens if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.²²

AZT/3TC is one of two recommended first-line NRTI (the other being ABC/3TC) for infants and children younger than three years of age, together with either LPV/r or NVP. For children between three and 12 years of age and adolescents, AZT/3TC is the second preferred option.²²

Paediatrics

There are four WHO-prequalified generic sources of the 60/30mg tablet. The Ranbaxy product is dispersible, making it suitable for children.

Patents

As none of the individual components are currently patented in India, this combination is produced by several Indian generic companies.

However, these generic versions came under threat in 2005 when India began granting patents on pharmaceuticals and GlaxoSmithKline

(GSK) applied for a patent on the combination.^{263, 264} Civil society organisations in India opposed the patent application in March 2006;²⁶⁵ this resulted in GSK announcing in August 2006 the withdrawal of all patent applications in all countries specifically related to this fixed-dose combination.²⁶⁶

The patent on 3TC in China expired in 2011. The generic version has since largely replaced ViV's product in the national free ART programme. Generic versions of AZT/3TC have been registered in China, but the national ART programme currently does not procure this combination. However, for paediatric patients, the programme still relies on the ViV product.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



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

GENERAL INFORMATION

- Therapeutic class: Three nucleoside reverse transcriptase inhibitors (NRTIs) in a triple fixed-dose combination.
- 2013 WHO Guidelines: AZT/3TC/ABC is recommended as an option for HIV-infected infants and children below the age of three who develop tuberculosis (TB) while on an ART regimen containing NVP or LPV/r. Children older than the age of three who are on TB treatment can also switch to AZT/3TC/ABC if they were an ART regimen containing NVP or a protease inhibitor.²²
- 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 approved by US Food and Drug Administration (FDA): November 2000.²³
- WHO Model List of Essential Medicines (EML): Not included. AZT, 3TC and ABC are included as stand-alone products in the 18th edition for adults and the 4th edition for children.^{24, 25} 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.²⁵⁴
- World sales of originator product: 2012: US\$162 million; 2011: \$204 million; 2010: \$233 million; 2009: \$307 million; 2008: \$350 million; 2007: \$455 million; 2006: \$529 million; 2005: \$598 million; 2004: \$635 million.^{26, 27, 28, 29, 30, 31, 141, 142, 143}
- Patents: Patents on AZT, 3TC, AZT/3TC or ABC also affect this combination. GSK also received a patent specifically related to the fixed-dose combination which is due to expire in 2016.³⁹

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

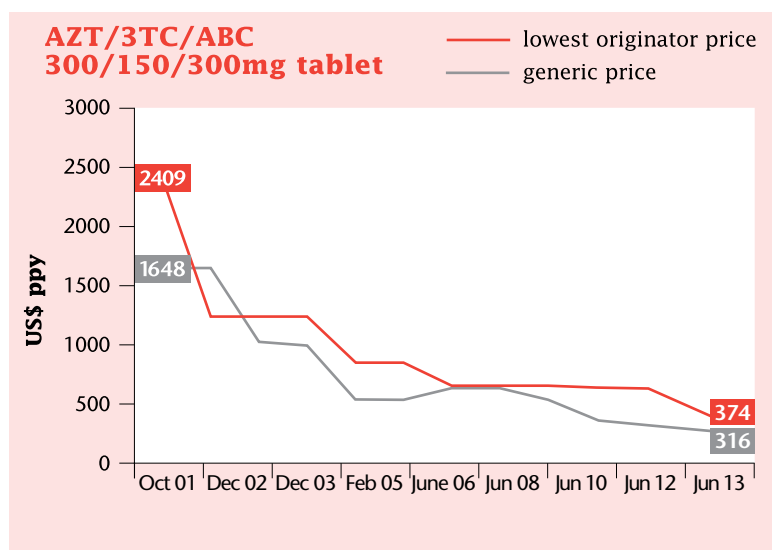
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Mylan	Ranbaxy
AZT/3TC/ABC 300/150/300mg tablet	2	374 (0.512)	341 (0.467)	316 (0.433)

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

As of May 2013, two generic sources of AZT/3TC/ABC 300/150/300mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 84% and the generic price has dropped by 81%.



SPOTLIGHT ON ACCESS ISSUES

This fixed-dose combination is the only triple-NRTI formulation available.

This combination is no longer a preferred regimen in the developed world, where its use is limited to individuals with contraindication to NNRTI-based regimens or who are unable to tolerate them.

There are two WHO-prequalified generic sources of this drug, but price remains an issue.

WHO Guidelines

In infants and children younger than three years of age, AZT/3TC/ABC is recommended for children who develop tuberculosis (TB), while on a regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the child put back on the original regimen.

Children three years of age and older on an NVP- or PI-based treatment can switch to a triple-NRTI regimen.²²

Paediatrics

There is one WHO-prequalified generic manufacturer of the paediatric formulation, but the company chose not to provide any pricing information.

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 before the full implementation of the TRIPS agreement.

This allowed generic versions of each medicine and the combination to be produced in India. However,

generic versions of AZT/3TC/ABC came under threat when India began granting patents on pharmaceuticals in 2005 and GlaxoSmithKline (GSK) applied for a patent on the combination. Civil society organisations in India opposed the patent application in March 2006;²⁶⁵ this resulted in GSK announcing in August 2006 the withdrawal of all patent applications in all countries specifically related to this fixed-dose combination.²⁶⁶

GSK holds patents on the combination of AZT with 3TC or ABC in several countries, including in China, Russia, and in OAPI and ARIPO countries.³⁹

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



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

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a triple fixed-dose combination.
- 2013 WHO Guidelines: AZT/3TC/NVP is recommended as an alternative first-line treatment for children, adolescents, and adults.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on AZT, 3TC and NVP meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 18th edition for adults and the 4th edition for children.^{24, 25} 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.²⁵⁴
- World sales of originator product: not applicable.
- Patents: Patents related to AZT, 3TC, AZT/3TC and to 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 unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to annex 2 for the incoterms associated with these prices.

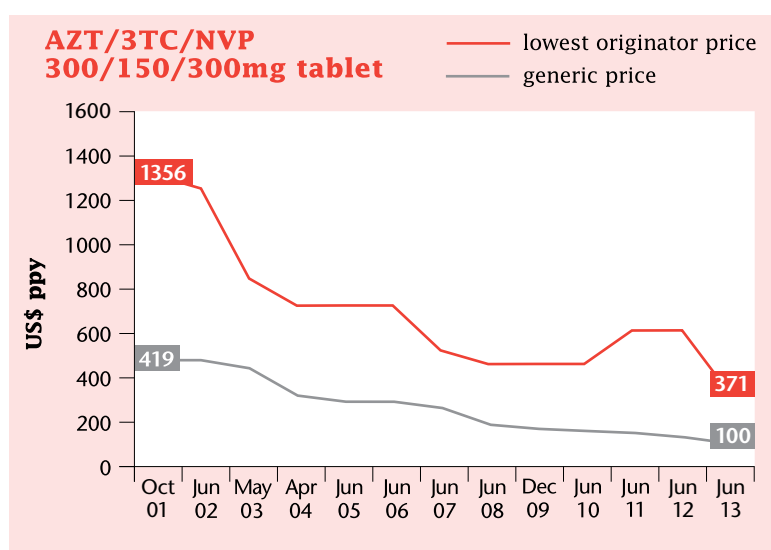
	Daily dose	Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy	Strides
AZT/3TC/NVP 60/30/50mg tablet (paediatrics)	4		119 (0.082)		101 (0.069)			97 (0.067)
AZT/3TC/NVP 300/150/200mg tablet	2	101 (0.138)	116 (0.158)	110 (0.150)	100 (0.138)	156 (0.214)	108 (0.148)	103 (0.142)

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

As of May 2013, seven generic sources of AZT/3TC/NVP 300/150/200mg tablet are quality-assured by US FDA or WHO prequalification. 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 originator AZT/3TC fixed-dose combination and the originator nevirapine single formulation.

Since 2002, the originator price has decreased by 70% whereas the generic price has dropped by 76%.



SPOTLIGHT ON ACCESS ISSUES

WHO Guidelines

AZT/3TC/NVP is an alternative first-line ART regimen for adolescents, pregnant and breastfeeding women, adults and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV), when TDF-based regimens are not available or contraindicated.²²

WHO guidelines recommend EFV-based regimens as the preferred first-line treatment options for pregnant women, regardless of trimester stage, and women of reproductive age.²² WHO advice also states the programmatic consequences of avoiding EFV use in pregnancy and supports its use as part of a simplified first-line treatment.

AZT/3TC/NVP is one of the first-line ART regimens recommended for children over three years of age.²²

Paediatrics

Two additional manufacturers received prequalification of AZT/3TC/NVP 60/30/50mg products at the end of 2012, bringing the current total of prequalified manufacturers to three.

Patents

There is no originator AZT/3TC/NVP fixed-dose combination.

In early 2004, when generic versions of AZT/3TC/NVP did not exist, MSF approached Canadian generic company Apotex to develop the combination and export it under compulsory licence to an individual developing country with no manufacturing capacity. As well as securing access to additional treatment options, the objective was to test the 'August 30 Decision', adopted by the World Trade Organization in 2003, and which Canada had recently signed into national law.²⁶⁷

The purpose of the August 30 Decision is to find an 'expeditious solution' to the problem faced by developing countries with no or insufficient manufacturing capacity. Such countries must rely on importing medicines produced in, and exported from, other countries – if the medicines are patented in producing countries, the only option would be for a compulsory licence to be issued. The August 30

Decision was thus the WTO's attempt to create a procedure for medicines to be exported under compulsory licence.²⁶⁸

Apotex did manufacture AZT/3TC/NVP, and succeeded in exporting to Rwanda under the August 30 Decision. However, because the company was hampered by the excessively bureaucratic procedural requirements of the new WTO rules on compulsory licences for export, this did not happen until 2008 and 2009.²⁶⁹ In the meantime, the combination had been developed by manufacturers in India, free from these administrative obstacles.

The experience illustrates the excessive complexity of the August 30 Decision, and how WTO member states should reform the mechanism, as it is currently far from providing an adequate solution to the needs to developing countries without a manufacturing capacity.

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.



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

GENERAL INFORMATION

- Therapeutic class: Two nucleoside reverse transcriptase inhibitors (NRTIs) in a double fixed-dose combination, with one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a co-pack.
- 2013 WHO Guidelines: AZT/3TC + EFV is recommended for first-line treatment for adults, pregnant and breast-feeding women and adolescents.²²
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on AZT, 3TC and EFV meant that generic companies were able to produce this therapeutically interesting fixed-dose combination.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Not included. AZT, 3TC and EFV medicines are included as stand-alone products in the 18th edition for adults and the 4th edition for children.^{24, 25} 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.²⁵⁴
- World sales of originator product: not applicable.
- Patents: Patents related to AZT, 3TC, AZT/3TC or to EFV also affect this combination. Cipla applied for patents specifically related to the use of AZT, 3TC and EFV in combination which will not expire before 2013 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 unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2013) are in **bold**.

Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

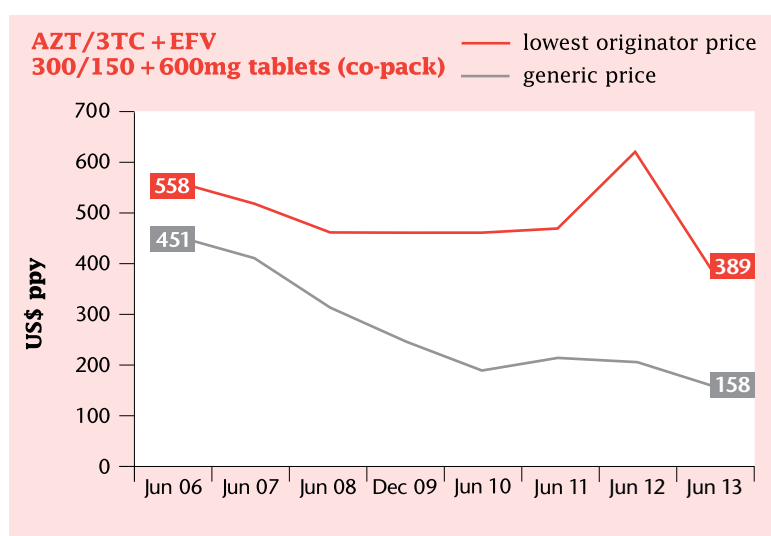
	Daily dose	Aurobindo	Hetero	Micro Labs	Ranbaxy
AZT/3TC + EFV 300/150 + 600mg tablets (co-pack)	1 kit (3 tablets)	158 (0.433)	225 (0.617)	292 (0.800)	233 (0.639)

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

As of May 2013, two generic sources of AZT/3TC + EFV 300/150 + 600mg tablets (co-pack) are quality-assured by US FDA or WHO prequalification. 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 originator AZT/3TC fixed-dose combination and the originator efavirenz single formulation.

Since 2006, the generic price has decreased by 65%. Since 2011, the originator price has decreased by 37%.



SPOTLIGHT ON ACCESS ISSUES

This combination is not available as a fixed-dose combination.

WHO Guidelines

AZT/3TC + EFV is an alternative first-line ART regimen for adolescents, pregnant and breastfeeding women, adults and people who are co-infected with tuberculosis (TB) or hepatitis B virus (HBV), when TDF-based regimens are not available or contraindicated.²²

TDF-based regimens are preferred over AZT-based regimens if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.²²

WHO guidelines recommend EFV-based regimens as the preferred first-line treatment options for pregnant women, regardless of trimester stage, and women of reproductive age. WHO advice also states the

programmatic consequences of avoiding EFV use in pregnancy and supports its use as part of a simplified first-line treatment.

AZT/3TC + EFV is recommended as a second-line ART regimen for children three years of age and older when LPV/r with ABC was used as first-line treatment.²²

For children over three years of age and co-infected with TB, the preferred regimen is EFV and two NRTIs.²²

Paediatrics

Toxicity risks are associated with AZT, with possible anaemia developing over the first few months of therapy, however the drug remains much better tolerated than d4T.²²

Currently a co-pack of AZT/3TC + EFV for children does not exist. Please refer to the AZT/3TC and the EFV drug profiles for additional

information on available paediatric formulations and strengths.

Patents

There is no originator AZT/3TC + EFV co-pack.

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 before the full implementation of the TRIPS agreement. This allowed Indian drug companies to manufacture generic versions of the medicines and to produce this co-pack.

A patent on AZT/3TC was granted in ARIPO and OAPI countries but has been officially withdrawn by GSK.³⁹

Please refer to the individual drug profiles for further information about patent barriers relating to the drugs in this combination.

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 included in the WHO List of Prequalified Medicinal Products (as of May 2013) are in **bold**. Shaded products are paediatric formulations. Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies								
Abacavir (ABC)		ViiV		Aspen	Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides		
20mg/ml oral solution	12 ml	355 (0.081)		96 (0.022)	237 (0.054)	173 (0.040)	158 (0.036)					
60mg tablet	4					146 (0.100)		122 (0.083)				
300mg tablet	2	222 (0.304)		172 (0.236)	152 (0.208)	170 (0.233)	153 (0.210)	149 (0.204)	189 (0.258)	256 (0.350)		
Atazanavir (ATV)		Bristol-Myers Squibb (BMS)		Emcure	Hetero	Mylan						
		Category 1 countries	Category 2 countries									
100mg capsule	xx			(0.267)								
150mg capsule	2	412 (0.564)	412 (0.564)	268 (0.367)								
200mg capsule	xx	(0.677)	(0.677)	(0.483)								
300mg capsule	1			268 (0.733)	256 (0.700)	195 (0.533)						
Atazanavir/ritonavir (ATV/r)				Mylan								
300/100mg tablet	1			219 (0.600)								
Darunavir (DRV)		Janssen		Aspen	Hetero							
300mg tablet	4	810 (0.555)		861 (0.589)								
400mg tablet	2				730 (1.000)							
600mg tablet	2	810 (1.110)			1095 (1.500)							
Didanosine (ddl)		Bristol-Myers Squibb (BMS)										
		Category 1 countries	Category 2 countries									
2g powder for reconstitution (final concentration 10mg/ml)	12ml	233 (0.053)	case-by-case basis									
25mg tablet	6	256 (0.117)	case-by-case basis									
100mg tablet	xx	(0.213)	case-by-case basis									
Efavirenz (EFV)		Merck		Aurobindo	Cipla	Emcure	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides
		Category 1 countries	Category 2 countries									
30mg/ml suspension	xx	(0.094)	case-by-case basis									
50mg capsule	xx			(0.075)				(0.073)				
50mg tablet	xx	(0.114)	case-by-case basis									
100mg dispersible tablet	xx											
200mg capsule	3			77 (0.070)	73 (0.067)			66 (0.060)			63 (0.058)	
200mg tablet	3	394 (0.360)	case-by-case basis									113 (0.103)
600mg tablet	1	237 (0.650)	case-by-case basis	40 (0.110)	49 (0.133)	61 (0.167)	47 (0.130)	43 (0.117)	49 (0.133)	39 (0.106)	43 (0.117)	41 (0.112)

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies													
Emtricitabine (FTC)				Cipla													
200mg capsule	1			73 (0.200)													
Etravirine (ETV)		Janssen		Aspen													
100mg tablet	4	438 (0.300)		467 (0.320)													
Lamivudine (3TC)		ViiV		Alkem	Aspen	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy	Strides					
10mg/ml oral suspension	10ml	171 (0.047)				28 (0.008)	30 (0.008)	37 (0.010)									
150mg tablet	2	75 (0.103)		44 (0.060)	26 (0.036)	27 (0.037)	30 (0.042)	26 (0.036)	24 (0.033)	29 (0.040)	24 (0.033)	28 (0.038)					
300mg tablet	1						37 (0.100)		21 (0.058)	61 (0.167)							
Lopinavir/ritonavir (LPV/r)		AbbVie (Abbott)		Aurobindo	Cipla	Hetero	Mylan										
		Category 1 countries	Category 2 countries														
80/20mg/ml oral solution	4ml	147 (0.101)	296 (0.203)		292 (0.200)												
100/25mg heat-stable tablet	3	108 (0.099)	278 (0.254)	150 (0.137)	183 (0.167)												
200/50mg heat-stable tablet	4	265 (0.182)	740 (0.507)	268 (0.183)	389 (0.267)	304 (0.267)	268 (0.183)										
Nevirapine (NVP)		Boehringer Ingelheim		Aspen	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides	Universal Corporation				
		Category 1 countries	Category 2 countries														
10mg/ml suspension	20ml	380 (0.052)	532 (0.073)		61 (0.008)	64 (0.009)											
50mg tablet for oral suspension	4				75 (0.052)	55 (0.038)											
200mg capsule	2																33 (0.045)
200mg tablet	2	219 (0.300)	438 (0.600)	31 (0.042)	28 (0.038)	33 (0.044)	29 (0.040)	29 (0.040)	29 (0.040)	44 (0.061)	30 (0.042)	29 (0.040)					
Raltegravir (RAL)		Merck															
		Category 1 countries	Category 2 countries														
400mg tablet	2	675 (0.925)	case-by-case basis														
Ritonavir (RTV)		AbbVie (Abbott)		Cipla	Mylan												
		Category 1 countries	Category 2 countries														
80mg/ml oral solution	xx	(0.091)	case-by-case basis														
100mg heat-stable tablet	2	83 (0.114)	case-by-case basis	316 (0.433)	178 (0.243)												
Tenofovir (TDF)		Gilead		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides								
		Category 1 countries	Category 2 countries														
300mg tablet	1	207 (0.567)	365 (1.000)	55 (0.150)	61 (0.167)	48 (0.132)	49 (0.133)	55 (0.150)	57 (0.157)								

Continued overleaf ⇨

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies							
Zidovudine (AZT)		ViiV		Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy		
10mg/ml oral solution	24 ml	399 (0.046)		91 (0.010)	78 (0.009)	100 (0.011)					
60mg tablet	4				96 (0.066)		43 (0.029)				
100mg capsule	xx	(0.102)		(0.046)	(0.050)						
250mg capsule	xx	(0.159)									
300mg tablet	2			73 (0.100)	79 (0.108)	79 (0.108)	70 (0.096)	85 (0.117)	71 (0.097)		
ABC/3TC		ViiV		Aurobindo	Cipla	Mylan					
60/30mg tablet	4			229 (0.157)	170 (0.117)	128 (0.088)					
600/300mg tablet	1	228 (0.624)		219 (0.600)	219 (0.600)	195 (0.533)					
d4T/3TC				Cipla	Hetero	Mylan	Ranbaxy	Strides			
6/30mg dispersible tablet	4			46 (0.032)							
12/60mg dispersible tablet	2			40 (0.055)							
30/150mg tablet	2			41 (0.056)	39 (0.053)	43 (0.058)	33 (0.046)	36 (0.049)			
d4T/3TC/NVP				Cipla	Hetero	Mylan	Ranbaxy	Strides			
6/30/50mg dispersible tablet	4			56 (0.038)							
12/60/100mg dispersible tablet	2			52 (0.072)							
30/150/200mg tablet	2			55 (0.075)	59 (0.081)	64 (0.088)	62 (0.085)	58 (0.079)			
TDF/FTC		Gilead		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy			
		Category 1 countries	Category 2 countries								
300/200mg tablet	1	319 (0.875)	548 (1.500)	74 (0.203)	110 (0.300)	79 (0.217)	74 (0.203)	110 (0.300)			
TDF/FTC/EFV		Merck		Aspen	Aurobindo	Cipla	Hetero	Mylan	Ranbaxy		
		Category 1 countries	Category 2 countries								
300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	139 (0.381)	170 (0.467)	158 (0.433)	137 (0.375)	161 (0.442)	164 (0.450)		
TDF/3TC				Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy		
300/300mg tablet	1			57 (0.157)	85 (0.233)	64 (0.177)	63 (0.173)	103 (0.281)	69 (0.188)		
TDF/3TC/EFV				Aurobindo	Cipla	Hetero	Mylan				
300/300/600mg tablet	1			152 (0.417)	134 (0.367)	139 (0.382)	149 (0.408)				
TDF/3TC + NVP (co-pack)				Hetero	Mylan						
300/300 + 200mg co-pack	1 kit (3 tabs)			122 (0.333)	113 (0.308)						
AZT/3TC		ViiV		Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Universal Corporation
60/30mg tablet	4			56 (0.038)	73 (0.050)			55 (0.038)		73 (0.050)	
300/150mg tablet	2	152 (0.208)		84 (0.115)	91 (0.125)	93 (0.128)	88 (0.121)	85 (0.117)	125 (0.115)	84 (0.115)	92 (0.127)
AZT/3TC/ABC		ViiV		Mylan	Ranbaxy						
300/150/300mg tablet	2	374 (0.512)		341 (0.467)	316 (0.433)						
AZT/3TC/NVP				Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy	Strides	
60/30/50mg tablet	4				119 (0.082)		101 (0.069)			97 (0.067)	
300/150/200mg tablet	2			101 (0.138)	116 (0.158)	110 (0.150)	100 (0.138)	156 (0.214)	108 (0.148)	103 (0.142)	
AZT/3TC + EFV (co-pack)				Aurobindo	Hetero	Micro Labs	Ranbaxy				
300/150 + 600mg tablets (co-packs)	1 kit (3 tabs)			158 (0.433)	225 (0.617)	292 (0.800)	233 (0.639)				

ANNEX 2: WHICH COUNTRIES CAN ACCESS THE QUOTED PRICES? CONDITIONS OF OFFER, AS QUOTED BY ORIGINATOR AND GENERIC 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. This lack of uniformity leads to significant differences in the eligibility of a country for different products. Some companies resort to the least-developed country (LDC) classification developed by the United Nations (which are updated every few years), others to World Bank classifications concerning country income (which are updated annually), others still to geographical criteria (which may be subjective). Lists provided by companies may differ from the classifications developed by the United Nations or the World Bank.

The conditions detailed in the table below were those quoted by companies, unless otherwise specified.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
AbbVie (Abbott)	<p>Category 1 countries: All African countries and all United Nations-defined least-developed countries outside Africa. The following list of countries was provided by AbbVie:</p> <p>Afghanistan, Algeria, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, 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, Timor-Leste, Togo, Tunisia, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe.</p> <p>Category 2 countries: The following list of countries was provided by AbbVie:</p> <p>Albania, Armenia, Azerbaijan, Belarus, Bolivia, Bosnia and Herzegovina, China, Colombia, Dominican Republic, Ecuador, El Salvador, Fiji, Georgia, Guatemala, Guyana, Honduras, India, Indonesia, Jamaica, Jordan, Kazakhstan, Kyrgyzstan, Macedonia, Marshall Islands, Micronesia, Moldova, Mongolia, Montenegro, Nicaragua, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Serbia, Sri Lanka, Suriname, Syria, Tajikistan, Thailand, Tonga, Turkmenistan, Ukraine, Uzbekistan, Viet Nam.</p>	Governments and programmes fully funded by governments, UN systems organisations, non-governmental organisations and other not-for-profit institutional providers in low- and lower middle-income countries.		FOB Netherlands.
Alkem	No restrictions.	No restrictions.		FCA Mumbai.
Aspen	South Africa.	South African tender authorities (i.e. public sector only).		Ex-works.
Aurobindo	No restrictions.	No restrictions.	Minimum quantity and freight & insurance additional as per incoterms, mode of shipment and destination.	Ex-works.

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Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Boehringer Ingelheim (BI)	<p>Category 1 countries: All least-developed countries, all low-income countries and all of Africa. Based on this definition, and according to the classifications of least-developed countries by the United Nations and low-income economies by the World Bank, the following countries should be covered:</p> <p>Afghanistan, Algeria, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, North Korea, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, São Tomé and Príncipe, Senegal, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tajikistan, Tanzania, Timor-Leste, Togo, Tunisia, Tuvalu, Uganda, Tanzania, Vanuatu, Yemen, Zambia, Zimbabwe.</p> <p>Category 2 countries: All middle-income countries not covered under Category 1. Based on this definition, and according to the classifications of middle-income economies by the World Bank, the following countries should be covered:</p> <p>Albania, American Samoa, Antigua and Barbuda, Argentina, Armenia, Azerbaijan, Belarus, Belize, Bhutan, Bolivia, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Fiji, Georgia, Grenada, Guatemala, Guyana, Honduras, India, Indonesia, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Kiribati, Kosovo, Laos, Latvia, Lebanon, Libya, Lithuania, Macedonia, Malaysia, Maldives, Marshall Islands, Mauritius, Mexico, Micronesia, Moldova, Mongolia, Montenegro, Nicaragua, Pakistan, Palau, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Romania, Russia, Serbia, Seychelles, Solomon Islands, Sri Lanka, St Lucia, St. Vincent and the Grenadines, Suriname, Syria, Thailand, Tonga, Turkey, Turkmenistan, Ukraine, Uruguay, Uzbekistan, Venezuela, Viet Nam, West Bank and Gaza.</p>	Governments, non-governmental organisations and other partners "who can guarantee that the programme is run in a responsible manner".		CIF to country (nearest international airport).
Bristol-Myers Squibb (BMS)	<p>Category 1 countries: Sub-Saharan African countries (with the exception of Southern African countries) plus countries classified as low-income by the World Bank (except Korea, Kyrgyzstan, Moldova and Uzbekistan). The following list of countries was provided by BMS:</p> <p>Afghanistan, Angola, Bangladesh, Benin, Bhutan, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), 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, Viet Nam, Yemen.</p> <p>Category 2 countries: Southern African countries. The following list of countries was provided by BMS:</p> <p>Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia, Zimbabwe.</p> <p>For other developing countries, prices are negotiated on a case-by-case basis with local BMS representatives.</p>	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.	FCA Rome.
Cipla	No restrictions.	Ministries of Health, public sector buyers.		Ex-works Mumbai.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Emcure	Atazanavir is restricted to sales in India and sub-Saharan Africa. No restrictions for other ARVs.	No restrictions.		Ex-works.
Gilead	Category 1 countries: 111 eligible countries, including all African states and additional countries based on a country's economic status, measured by gross national income (GNI) and HIV prevalence. The following list was provided by Gilead: Afghanistan, Algeria, Angola, Anguilla, Antigua and Barbuda, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, Botswana, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Cayman Islands, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Cuba, Curacao, 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, South Sudan, St. Maarten, 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: 24 eligible countries based on a country's economic status, measured by gross national income (GNI) and HIV prevalence. The following list was provided by Gilead: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, China, Ecuador, El Salvador, Fiji, Georgia, Iran, Iraq, Jordan, Kazakhstan, Montenegro, Kosovo, Panama, Paraguay, Peru, Philippines, Sri Lanka, Thailand, Tonga, Turkmenistan.	No restrictions.	Prices quoted here are Gilead prices to distributors.	FOB Dublin.
Hetero	No restrictions.	Private sector, public sector and non-governmental organisations.	Prices may be negotiated on individual basis according to commercial terms.	FOB Mumbai.
Janssen (Johnson & Johnson)	Category 1 countries: All countries in sub-Saharan Africa and all least-developed countries outside of Africa. The following list was provided by Janssen: Afghanistan, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central Africa Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Laos, Lesotho, Liberia, Maldives, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Timor-Leste, Togo, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe. For other low- and middle-income countries, differentiated prices are applicable and negotiated on a case-by-case basis.	Category 1 countries: no restrictions with respect to eligibility. Category 2 countries: case-by-case basis.	Supply is ensured through Aspen Pharmacare sub-Saharan Africa and by Janssen in least-developed countries. Paediatric formulations of darunavir and etravirine are being made available on a compassionate use basis.	FOB Johannesburg for sub-Saharan Africa. FOB Italy for least-developed countries.

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Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Merck	<p><i>For efavirenz and raltegravir – Category 1 countries:</i> All countries in sub-Saharan Africa and low-income countries based on World Bank country classification. The following list was provided by Merck:</p> <p>Afghanistan, Angola, Bangladesh, Benin, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, The, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, North Korea, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mayotte, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tajikistan, Tanzania, Togo, Uganda, Zambia, Zimbabwe.</p> <p><i>Category 2 countries:</i> 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 high-income countries. These prices will vary based on country income, disease burden, and will be negotiated on a case-by-case basis with each government. Low- and middle-income countries that are members of the European Union are not eligible for these prices.</p> <p><i>For TDF/FTC/EFV – Category 1 countries:</i> The following list was provided by Merck:</p> <p>Afghanistan, Angola, Antigua and Barbuda, Bangladesh, Belize, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), 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, Samoa, Sudan, Suriname, Swaziland, Tanzania, Timor-Leste, Togo, Trinidad and Tobago, Tuvalu, Uganda, Ukraine, Vanuatu, Yemen, Zambia, Zimbabwe.</p> <p><i>Category 2 countries:</i> The following list was provided by Merck:</p> <p>Bolivia, Indonesia, Kyrgyzstan, Mauritius, Mongolia, Nicaragua, Seychelles, Syria, Tajikistan, Uzbekistan, Viet Nam.</p>	<p>Governments and programmes fully funded by governments and/or by multi- and bi-lateral donors (i.e. the Global Fund, PEPFAR, or UNITAID), UN system organisations, non-governmental organisations and other non-commercial providers of HIV treatment.</p>		<p>CIP airport of destination basis.</p> <p>Additional costs may include freight, insurance, customs handling, taxes and duties.</p>
Micro Labs	No restrictions.	No restrictions.		Ex-works.
Mylan	<p><i>For tenofovir-based products:</i> Mylan has a licence for supplying 108 countries which cover sub-Saharan Africa, Latin America & the Asia-Pacific regions. The list of countries was not shared with MSF for the purpose of this publication. Delivery to other countries is done on a case-by-case basis.</p> <p><i>For atazanavir:</i> Mylan has a licence for supplying 46 countries. The list of countries was not shared with MSF for the purpose of this publication. Delivery to other countries is done on a case-by-case basis.</p> <p>For Belarus, Congo (DRC), Cuba, Iran, North Korea, Liberia, Myanmar, Sudan, and Syria, Mylan needs to apply for an OFAC licence with the US Treasury before proceeding with shipment.</p>	No restrictions.	Minimum order quantity: one full shipper.	FCA Mumbai.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Quality Chemicals	Burundi, Kenya, Rwanda, Tanzania and Uganda.	No restrictions.		DDP.
Ranbaxy	All low-income economies and countries included in the CHAI consortium. Based on this definition, and according to the classifications of low-income economies by the World Bank and the list of countries included in the CHAI consortium, the following countries should be covered: Afghanistan, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Central African Republic, Chad, Comoros, Congo (DRC), Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, North Korea, Kyrgyzstan, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Myanmar, Nepal, Niger, Rwanda, Sierra Leone, Somalia, Tajikistan, Tanzania, Togo, Uganda, Zimbabwe.	Ministries of Health and National AIDS control programmes, institutes affiliated with national health programmes, WHO, UNICEF, MSF, CHAI, PFSCM, IDA, PSI and other non-governmental organisations receiving Global Fund grants.	All these prices are tentative and will depend on the final order quantity.	Ex-works.
Strides Arcolab	Countries covered by PEPFAR and supported by Global Fund. The following list was provided by Strides: Angola, Antigua and Barbuda, Bahamas, Barbados, Belize, Botswana, Cambodia, Cameroon, China, Congo (DRC), Costa Rica, Côte d'Ivoire, Dominica, Dominican Republic, El Salvador, Ghana, Grenada, Guatemala, Guyana, Haiti, Honduras, India, Indonesia, Jamaica, Kazakhstan, Kenya, Kyrgyzstan, Laos, Lesotho, Malawi, Mozambique, Namibia, Nicaragua, Nigeria, Papua New Guinea, Panama, Russia, Rwanda, St. Kitts and Nevis, St. Lucia, St. Vincent, South Africa, South Sudan, Suriname, Swaziland, Tajikistan, Tanzania, Thailand, Trinidad and Tobago, Turkmenistan, Uganda, Ukraine, Uzbekistan, Vietnam, Zambia, Zimbabwe.	No restrictions.		FOB Bangalore, India.
Universal Corporation	No restrictions.	No restrictions.		Ex-works.
ViiV	Category 1 countries: All low-income countries, all least-developed countries and all of sub-Saharan Africa. Based on this definition, and according to the classifications of low-income economies by the World Bank, and least-developed countries by the United Nations, the following countries should be covered: Afghanistan, Angola, Bangladesh, Benin, Botswana, Bhutan, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, North Korea, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tajikistan, Tanzania, Timor-Leste, Togo, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe.	Ministries of Health; United Nations agencies; international procurement agencies and not-for-profit non-governmental organisations.		Ex-works. Other incoterms can be supplied on request.

ANNEX 3: SPOTLIGHT ON VOLUNTARY LICENCES

Originator pharmaceutical companies are increasingly using voluntary licences (VLs) and other similar instruments (such as non-assert covenants and immunity-from-suit agreements) to expand their operations through partnerships with generic manufacturers. A number of ARVs are now being produced under different forms of licensing arrangements between originator and generic producers.

The following table provides a non-exhaustive list of VLs signed by different companies.

The claim is that VLs facilitate the production of affordable ARVs in developing countries. There is, however, very little publically available information about these deals – in almost all cases (with the notable exception of licences negotiated through the Medicines Patent Pool), companies do not disclose full terms and conditions of voluntary arrangements. Terms and conditions

like the rate of royalty, clauses that govern active pharmaceutical ingredients (APIs) and formulations like fixed-dose combinations are shrouded in secrecy. As disclosure of terms and conditions is limited, the information provided below is piecemeal – in many cases, generic manufacturers do not even provide the specific territories to which the drug can be supplied or not supplied, even to procurers like MSF, citing confidentiality clauses in the VLs.

Separate agreements have also been signed between originator companies and the Government of Brazil, although only the terms of one agreement have been released after Brazilian civil society invoked access to information legislation.

Despite this limited access to information, a trend clearly emerges: that of originator companies restricting voluntary licences to least-developing countries and sub-Saharan Africa, and generally excluding lower middle- and middle-income countries (with the

notable exception of India, which is sometimes included). There is no VL that covers all developing countries – the geographical scope for different licences ranges from 48 territories covered to 118.

Another restriction is that licences are often provided to a limited list of manufacturers.

The table below also reveals how voluntary licences sometimes cover drugs which are not patented, or where patents have expired in most licenced territories. In such cases, the actual impact of these agreements on public health, transfer of technology and/or local production for both the APIs and the finished formulations becomes even more questionable until full terms are properly disclosed.

Claims as to the public health benefits of voluntary licensing arrangements can therefore not be verified until companies open their contractual terms and conditions for public scrutiny.

Voluntary licence	Comments
<p>VL between ViiV (GSK) and Aspen.</p>	<p>GEOGRAPHIC SCOPE: 69 countries are eligible: sub-Saharan Africa + least-developed countries + low-income countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: The ABC compound patent has already expired, but there is a possibility that these non-exclusive licences include formulation patents.</p>
<p>ABACAVIR (ABC)</p> <p>In February 2013, the Medicines Patent Pool (MPP) and ViiV announced a licence agreement covering paediatric ABC. This is ViiV's first licence with MPP. To date, however, there are no sub-licences reported by the MPP.</p> <p>MPP and ViiV also entered into a separate, non-binding Memorandum of Agreement, which promises collaboration on paediatric licensing of pipeline ARVs, development of novel combination paediatric formulations, and availability of novel paediatric formulations outside of the existing list of licensed territories.</p>	<p>GEOGRAPHIC SCOPE: 118 countries and territories. This licence provides the broadest geographical coverage of any VL. However, many developing countries are still excluded, such as China, Brazil, Mexico, Russia, Kazakhstan, Kyrgyzstan, and Ukraine (where GSK is actively enforcing its ABC-related patents against generic companies). This is concerning as it may set a precedent for future licences negotiated with ViiV.</p> <p>TRANSPARENCY: The full text is publicly available on the MPP website.</p> <p>OTHER TERMS AND CONDITIONS: In terms of royalty provisions and API restrictions, this licence provides improved terms and conditions compared to any other known voluntary licences.</p>

	Voluntary licence	Comments
ATAZANAVIR (ATV)	Bristol-Myers Squibb (BMS) licence agreements signed with Aspen, Emcure and Mylan. BMS has signed deals with three other companies, but their names are unknown.	<p>GEOGRAPHIC SCOPE: 48 countries: sub-Saharan Africa + India.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-free non-exclusive licences and immunity-from-suit agreements for manufacturing and distribution, including for paediatric formulations.</p>
	In October 2012, an agreement was signed between Bristol-Myers Squibb (BMS) and Farmanguinhos, a publicly-owned Brazilian laboratory.	<p>GEOGRAPHIC SCOPE: Limited to Brazil.</p> <p>TRANSPARENCY: The licence is not publically available.</p> <p>OTHER TERMS AND CONDITIONS: The agreement includes sub-licences for the exploitation of the patent, technology transfer and supply of 200 and 300mg ATV capsules. Farmanguinhos production is expected to begin in 2015 (assuming it can be registered) and to fulfil 50% of Ministry of Health demands for ATV for 2015-2017.</p> <p>By contrast to the above royalty-free VLs, the deal with Farmanguinhos provides for the payment of a 4.5% royalty. The expiry date of the patent covered in the agreement is 2017. Although the local production of this medicine can be a significant achievement for Brazilian industry and can help to improve its capacity, questions remains as to whether this agreement will really benefit patients, as the deal explicitly excludes fixed-dose combination ATV/r, and all other possible formulations or dosages from being produced. The price reduction achieved through the deal is limited, at 5% of the current price.</p>
COBICISTAT (COBI)	In 2011, Gilead signed an agreement with Medicines Patent Pool (MPP), authorising the MPP to grant sub-licences for manufacturing only for companies in India. The following sub-licencees in India currently have signed agreements with the MPP: Emcure, Aurobindo, MedChem, Hetero, Laurus Labs, and Shasun Pharma.	<p>GEOGRAPHIC SCOPE: The licences carry an India-specific manufacturing restriction with further limitation on territories to which drugs can be supplied. 103 territories are included. Countries such as China, Brazil, Ukraine, Sri Lanka, and Indonesia are excluded.</p> <p>TRANSPARENCY: The full text is publicly available on the MPP website.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive licence bearing a royalty of 5%, with no royalties on paediatric versions developed by licensees.</p>
	In 2011, in a separate arrangement to the one detailed above, Gilead signed semi-exclusive licences for the supply of COBI with four Indian manufacturers: <ul style="list-style-type: none"> • Matrix • Hetero • Ranbaxy • Strides. 	<p>GEOGRAPHIC SCOPE:</p> <p>The four licensees are given semi-exclusive rights over certain territories:</p> <ul style="list-style-type: none"> • Matrix: Sri Lanka, Thailand • Hetero and Ranbaxy: Botswana, Namibia • Strides: Ecuador, El Salvador, Indonesia, Kazakhstan, Turkmenistan. <p>In addition to these semi-exclusive territories, these 'preferred' licensees can also cover territories mentioned in Gilead-MPP licences detailed above.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Gilead will charge 10–15% royalties.</p>
DARUNAVIR (DRV)	In 2007, Janssen (Johnson & Johnson) signed a Special Access Branded Product agreement with Aspen to provide right to register, distribute and package (but not manufacture).	<p>GEOGRAPHIC SCOPE: 65 countries: sub-Saharan Africa + least-developed countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-free non-exclusive licences. Aspen will register, package and distribute DRV at a differential price.</p>
	In 2008, Janssen (Johnson & Johnson) signed a VL including manufacture of the product with Emcure.	<p>GEOGRAPHIC SCOPE: Limited to India.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-bearing licence (5% royalty rate), which also allows development of fixed-dose combinations and API manufacturing.*</p>
	A Public-Private Partnership agreement has recently been reached to manufacture and supply DRV in Brazil.	<p>GEOGRAPHIC SCOPE: Limited to Brazil.</p> <p>TRANSPARENCY: Details are not publicly known.</p> <p>OTHER TERMS AND CONDITIONS: No information is yet available.</p>

* For details see: http://www.janssenrnd.com/sites/default/files/pdf/Licensing_FINAL.pdf

	Voluntary licence	Comments
DIDANOSINE (ddI)	<p>Since 2001, BMS signed licence agreements allowing the following generic companies: Adcock-Ingram; Aspen; Danpong- Adams; Enaleni; Sonke; Varichem; Thembalani; AfrikaBiopharm; Aurobindo; Emcure; Ranbaxy, Mylan (Matrix).</p> <p>The agreements also cover stavudine (d4T).</p>	<p>GEOGRAPHIC SCOPE: 49 countries: sub-Saharan Africa + India.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: The agreements are royalty-free, include paediatric formulations.</p>
	<p>Since 2007, Merck signed licence agreements with the following companies: Emcure; Arrow; Sonke; Aspen Aurobindo; Cipla-Medpro; Adcock Ingram.</p>	<p>GEOGRAPHIC SCOPE: South Africa. There are no patents in other sub-Saharan African countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-free non-exclusive licences.</p>
ELVITEGRAVIR	<p>In 2011, Gilead signed an agreement with Medicines Patent Pool (MPP), authorising the MPP to grant sub-licences for manufacturing only for companies in India.</p> <p>The following sub-licensees in India currently have signed agreements with the MPP:</p> <ul style="list-style-type: none"> • Emcure • Aurobindo • MedChem • Hetero Labs • Laurus Labs • Shasun Pharma. 	<p>GEOGRAPHIC SCOPE: There is an India specific manufacturing restriction, with further limitation on territories where drugs can be supplied. 100 countries are covered. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p> <p>TRANSPARENCY: The full text is publicly available on the MPP website.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive royalty-bearing granted to the Medicines Patent Pool. Royalty of 5%; no royalties on paediatric versions developed by licensees.</p>
	<p>In 2011, in a separate arrangement, Gilead also signed semi-exclusive licences for the supply of elvitegravir with four Indian manufacturers.</p>	<p>GEOGRAPHIC SCOPE: The four licensees are given semi-exclusive rights over certain territories:</p> <ul style="list-style-type: none"> • Matrix: Sri Lanka, Thailand • Hetero and Ranbaxy: Botswana, Namibia • Strides: Ecuador, El Salvador, Indonesia, Kazakhstan, and Turkmenistan. <p>In addition to these semi-exclusive territories, these 'preferred' licensees can also cover territories mentioned in Gilead-MPP licences detailed above.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: As a part of the 2011 semi- exclusive licences with four 'preferred' Indian generic manufacturers, Gilead will charge 10–15% royalties.</p>
ETRAVIRINE (ETV)	<p>In 2009, Janssen (Johnson & Johnson) signed a licence agreement with Aspen and Emcure.</p>	<p>GEOGRAPHIC SCOPE: Sub-Saharan Africa and least-developed countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-free non-exclusive licence. Aspen will only register and distribute ETV formulations (i.e. with no manufacturing).</p>

	Voluntary licence	Comments
LAMIVUDINE (3TC)	<p>Since 2001, ViiV (GSK) has signed 13 licence agreements, including with the following companies:</p> <ul style="list-style-type: none"> • Aspen • Cipla Medpro • Feza • Thembalami • Biotech Laboratories • Sonke • Cosmos 	<p>GEOGRAPHIC SCOPE: 69 countries: sub-Saharan Africa + least-developed countries + low-income countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive licences. Some licences include a royalty of 5% on net sales conditions, others are royalty-free. In 2009, GSK waived all royalty fees for all sub-Saharan African countries. According to ViiV's website, all voluntary licences are now royalty-free.</p>
NEVIRAPINE (NVP)	<p>Since 2004, Boehringer Ingelheim (BI) has signed licence agreements with the following companies: Cosmos; Universal Pharmacy; Aspen; Gemini; Memphis; Cipla Medpro; Kimia Farma; Adcock Ingram/Ranbaxy (Thembalami).</p> <p>Since 2007, BI signed non-assert declarations with the following companies: Cosmos; Aspen; Biotech Laboratories; Memphis; Aurobindo; Cipla; Emcure; Strides.</p>	<p>GEOGRAPHIC SCOPE: 78 countries: least-developed countries + low-income countries + sub-Saharan Africa.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Initially, BI signed royalty-bearing licence agreements allowing for manufacturing. In 2007, BI changed its policy to non-assert declarations allowing distribution at no additional costs.</p> <p>The only condition for the non-assert licences is that licensees must produce WHO-prequalified NVP products.</p>
RALTEGRAVIR (RAL)	<p>Since 2011, Merck signed licence agreements with Emcure and Mylan (Matrix).</p>	<p>GEOGRAPHIC SCOPE: 60 countries: sub-Saharan Africa and low-income countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive licences.</p>
	<p>In Brazil a Public-Private Partnership agreement has been announced to manufacture and supply RAL for the domestic market.</p>	<p>GEOGRAPHIC SCOPE: Limited to Brazil.</p> <p>TRANSPARENCY: Detailed terms and conditions are not known.</p> <p>OTHER TERMS AND CONDITIONS: No information is available.</p>
RILPIVIRINE	<p>Since 2011, Janssen (Johnson & Johnson) has signed two different types of licence agreements:</p> <ul style="list-style-type: none"> • First, a Special Access Branded Product agreement was signed in 2007 with Aspen to provide right to register, distribute and package (but not manufacture) • Second, a manufacturing the formulation was signed in 2008 with Emcure, Hetero, Mylan (Matrix) and Strides. 	<p>GEOGRAPHIC SCOPE: Originally 66 countries: sub-Saharan Africa + least-developed countries + India. Expanded in late 2011 to include 112 countries. The generic pharmaceutical manufacturers in India will have rights to market the product in sub-Saharan Africa, least-developed countries and India. Aspen will have rights to market the product in sub-Saharan Africa including South Africa.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: The licence to Aspen is royalty-free, with other terms and conditions not known. With other companies, Janssen signed royalty-bearing (2–5% royalty rate) voluntary non-exclusive licence. Licensees will manufacture, register, market and distribute rilpivirine both as a single agent and fixed-dose combination. The licence also allows development of FDCs and API manufacturing.</p>
SAQUINAVIR (SQV)	<p>Since 2006, Roche signed licence agreements with the following companies: Adcock Ingram; Addis; Aspen; Beximco; CAPS; Cosmos; Muhimbili University; Radiant; Regal; Shelys; Universal Corporation; Varichem; Zenufa.</p>	<p>GEOGRAPHIC SCOPE: Sub-Saharan Africa and least-developed countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: No information is available.</p>
STAVUDINE (d4T)	<p>Since 2001, Bristol-Myers Squibb (BMS) signed licence agreements with the following companies: Adcock Ingram; Aspen; Danpong- Adams; Enaleni; Sonke; Varichem; Thembalami; Afrika Biopharm; Aurobindo; Emcure; Ranbaxy.</p> <p>The agreements also cover didanosine (ddl).</p>	<p>GEOGRAPHIC SCOPE: 49 countries: sub-Saharan Africa + India.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: 11 immunity-from-suit agreements allowing generic companies to produce d4T and ddl. The agreements are royalty-free, and include paediatric formulations.</p>

	Voluntary licence	Comments
TENOFIVIR (TDF)	<p>Since 2006, Gilead signed licence agreements with the following companies: Aspen; Alkem; Cadila; Emcure; Hetero; Matrix (Mylan); McNeil & Argus; Medchem; Micro Labs; Ranbaxy; Sequent Scientific; Shasun; Strides.</p> <p>Gilead's 2006 licences were signed when opposition proceedings before Indian patent office were pending. One generic manufacturer, Cipla, decided not to sign this deal and continued manufacturing this drug.</p> <p>The TDF patent in India was eventually rejected but 2006 licensees nevertheless continued working under the arrangements with Gilead.</p>	<p>GEOGRAPHIC SCOPE: Originally 95 countries and territories, expanded in July 2011 to 112 countries and territories.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive royalty-bearing licences. The royalty rate of 5% lowered to 3% in July 2011; no royalties on paediatric versions developed by licensees.</p>
	<p>In 2011, Gilead signed an agreement with Medicines Patent Pool (MPP), authorising the MPP to grant sub-licences for manufacturing only for companies in India.</p> <p>Aurobindo, Shasun and Emcure are now sub-licensees to the MPP.</p>	<p>GEOGRAPHIC SCOPE: The licences carry an India-specific manufacturing restriction with further limitation on territories to which drugs can be supplied. The 2011 Gilead-Medicines Patent Pool licence for TDF product covers the same 112 countries territories as above. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p> <p>TRANSPARENCY: The full terms of the Gilead-MPP licences are publicly available.</p> <p>OTHER TERMS AND CONDITIONS: A key provision in the Gilead-MPP licence permits a licensee to terminate the licence on a drug-by-drug basis. Aurobindo, Shasun and Emcure, who had originally signed the 2006 licences, took advantage of this clause to terminate part of the 2006 licence in relation to TDF. These companies are now free to supply TDF without paying royalty to Gilead under the 2006 licence.</p> <p>For a review by MSF of the terms of this licence please see: http://www.msfacecess.org/content/msf-review-july-2011-gilead-licences-medicines-patent-pool</p>
ZIDOUVUDINE (AZT)	<p>Since 2001, ViiV (GSK) has signed 13 licence agreements, including with the following companies: Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos.</p>	<p>GEOGRAPHIC SCOPE: 69 countries: sub-Saharan Africa + least-developed countries + low-income countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive licences. Some licences include a royalty of 5% on net sales conditions, others are royalty-free. In 2009, GSK waived all royalty fees for all sub-Saharan African countries. According to ViiV's website, all voluntary licences are now royalty-free.</p>
3TC/AZT	<p>Since 2001, ViiV (GSK) has signed 13 licence agreements, including with the following companies: Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos.</p>	<p>GEOGRAPHIC SCOPE: 69 countries: sub-Saharan Africa + least-developed countries + low-income countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive licences. Some licences include a royalty of 5% on net sales conditions, others are royalty-free. In 2009, GSK waived all royalty fees for all sub-Saharan African countries. According to ViiV's website, all voluntary licences are now royalty-free.</p>
RILPIVIRINE/TDF/3TC	<p>Since 2011, Janssen (Johnson & Johnson) has signed licence agreements with the following companies:</p> <ul style="list-style-type: none"> • Aspen • Emcure • Hetero • Mylan (Matrix) • Strides 	<p>GEOGRAPHIC SCOPE: Originally 66 countries: sub-Saharan Africa + least-developed countries + India. Expanded in late 2011 to include 112 countries.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Royalty-bearing voluntary non-exclusive licence. The generic pharmaceutical manufacturers in India will have rights to market the product in sub-Saharan Africa, least-developed countries and India. Aspen will have rights to market the product in sub-Saharan Africa including South Africa. ²⁴⁷ Licensees will manufacture, register, market and distribute rilpivirine both as a single agent and fixed-dose combination.</p>

Voluntary licence	Comments
<p>TDF/FTC</p> <p>Since 2006, Gilead signed licence agreements with the following companies: Aspen; Alkem; Cadila; Emcure; Hetero; Matrix (Mylan); McNeil & Argus; Medchem; Micro Labs; Ranbaxy; Sequent Scientific; Shasun; Strides.</p> <p>Gilead's 2006 licence was signed when opposition proceedings before Indian patent office were pending. One generic manufacturer, Cipla, decided not to sign this deal and continued manufacturing this drug. The TDF patent in India was eventually rejected but 2006 licensees nevertheless continued working under previous arrangements with Gilead.</p>	<p>GEOGRAPHIC SCOPE: Originally 95 countries and territories, expanded in July 2011 to 112 countries and territories.</p> <p>TRANSPARENCY: Detailed terms and conditions are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive royalty-bearing licences. The royalty rate of 5% lowered to 3% in July 2011; no royalties on paediatric versions developed by licensees.</p>
<p>In 2011, Gilead signed an agreement with Medicines Patent Pool (MPP), authorising the MPP to grant sub-licences for manufacturing only for companies in India.</p> <p>Aurobindo, Shasun and Emcure are now sub-licensees to the MPP.</p>	<p>GEOGRAPHIC SCOPE: The licences carry an India-specific manufacturing restriction with further limitation on territories to which drugs can be supplied. The 2011 Gilead-MPP licence for TDF/FTC covers the same 112 countries territories as above. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p> <p>TRANSPARENCY: The full text is publicly available on the MPP website.</p> <p>OTHER TERMS AND CONDITIONS: A key provision in the Gilead-MPP licence permits a licensee to terminate the licence on a drug-by-drug basis. Aurobindo, Shasun and Emcure, who had originally signed the 2006 licences, took advantage of this clause to terminate part of the 2006 licence in relation to TDF. These companies are now free to supply TDF without paying royalty to Gilead under the 2006 licence.</p>
<p>THE 'QUAD' (TDF/FTC/COBI/ELVITEGRAVIR)</p> <p>In 2011, Gilead signed an agreement with Medicines Patent Pool (MPP), authorising the MPP to grant sub-licences for manufacturing for companies in India.</p> <p>The following sub-licensees in India currently have signed agreements with the MPP: Emcure; Aurobindo; MedChem; Hetero; Laurus Labs; Shasun Pharma.</p>	<p>GEOGRAPHIC SCOPE: There is an India-specific manufacturing restriction with further limitation on territories where drugs can be supplied. 100 countries and territories are covered. Countries such as China, Brazil, Ukraine, Sri Lanka, and Indonesia are excluded.</p> <p>TRANSPARENCY: The full text is publicly available on the MPP website.</p> <p>OTHER TERMS AND CONDITIONS: Non-exclusive royalty-bearing granted to the MPP. Royalty of 5%; no royalties on paediatric versions developed by licensees.</p>
<p>In 2011, in a separate arrangement to the one detailed above, Gilead signed semi-exclusive licences for the supply of the Quad with four Indian manufacturers:</p> <ul style="list-style-type: none"> • Matrix • Hetero • Ranbaxy • Strides. 	<p>GEOGRAPHIC SCOPE: The four licensees are given semi-exclusive rights over certain territories:</p> <ul style="list-style-type: none"> • Matrix: Sri Lanka, Thailand • Hetero and Ranbaxy: Botswana, Namibia • Strides: Ecuador, El Salvador, Indonesia, Kazakhstan, and Turkmenistan. <p>In addition to these semi-exclusive territories, these licensees can also cover territories mentioned in Gilead-MPP licences detailed above.</p> <p>TRANSPARENCY: Detailed terms and conditions of these licences are confidential.</p> <p>OTHER TERMS AND CONDITIONS: Gilead will charge 10–15% royalties.</p>

The information in the table was largely adapted from Peter Beyer, Developing socially responsible intellectual property licensing policies – non-exclusive licensing initiatives in the pharmaceutical sector in Jacques de Werra, Research Handbook on Intellectual Property Licensing, Edward Elgar Publishing, 2013.

In order to access the full text of voluntary licences signed by the Medicines Patent Pool (for paediatric ABC, COBI, elvitegravir, TDF, TDF/FTC, and the Quad), including the exact geographic scope of these licences and information on separate Gilead licences, please see: <http://www.medicinespatentpool.org>

ANNEX 4: COMPANY CONTACTS

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ANNEX 5: THE CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) CEILING PRICE LIST (AS OF MAY 2013)



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., Hetero Drugs, Mylan, Ranbaxy, Strides Arcolabs, Abbvie and Macleods. 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 Sunil Panicker at spanicker@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 overleaf 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.

Continued overleaf ❖❖❖

THE CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) CEILING PRICE LIST

ADULT PRODUCTS		2013 CEILING PRICE (USD)			SUPPLIER							
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides	Abbvie*	MacLeods
3TC (150mg)	HDPE bottle 60 tablets	\$28.8	\$2.4	\$0.04	✓ ²	✓ ¹	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ^{1,2}
ABC (300mg)	HDPE bottle 60 tablets	\$168	\$14	\$0.23	✓ ²	✓ ¹	✓ ²	✓ ^{1,2}				
AZT (300mg)	HDPE bottle 60 tablets	\$78	\$6.5	\$0.11	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			
AZT + 3TC (150mg/300mg)	HDPE bottle 60 tablets	\$91.2	\$7.6	\$0.13	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ^{1,2}
AZT + 3TC + NVP (300mg/150mg/200mg)	HDPE bottle 60 tablets	\$110.4	\$9.2	\$0.15	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ^{1,2}
d4T (30mg)	HDPE bottle 60 capsules	\$24	\$2.0	\$0.03	✓ ²	✓ ^{1,2}	✓ ²		✓ ¹			✓ ¹
d4T + 3TC (30mg/150mg)	HDPE bottle 60 tablets	\$45	\$3.75	\$0.06		✓ ^{1,2}	✓ ²					✓ ²
d4T + 3TC + NVP (30mg/150mg/200mg)	HDPE bottle 60 tablets	\$79	\$6.58	\$0.11		✓ ^{1,2}	✓ ^{1,2}					✓ ²
EFV (600mg)	HDPE bottle 30 tablets	\$48	\$4.0	\$0.13	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ^{1,2}
LPV/r (200/50mg)	HDPE bottle 120 tablets	\$300	\$25	\$0.21	✓ ²		✓ ^{1,2}	✓ ^{1,2}			✓ ²	
NVP (200mg)	HDPE bottle 60 tablets	\$36	\$3.0	\$0.05	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ^{1,2}
RTV (100mg) heat stable	HDPE bottle 30 tablets	\$90	\$7.5	\$0.25				✓ ¹				
TDF (300mg)	HDPE bottle 30 tablets	\$54	\$4.5	\$0.15	✓ ²		✓ ²	✓ ^{1,2}				✓ ¹
TDF + 3TC (300/300mg)	HDPE bottle 30 tablets	\$66	\$5.5	\$0.18	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹			✓ ²
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	\$75	\$6.25	\$0.21	✓ ²		✓ ²	✓ ^{1,2}				
TDF + 3TC + EFV (300/300/600mg)	HDPE bottle 30 tablets	\$130.8	\$10.9	\$0.36			✓ ²					
TDF + FTC + EFV (300/200/600mg)	HDPE bottle 30 tablets	\$156	\$13.0	\$0.43	✓ ²	✓ ¹	✓ ³	✓ ^{1,2}				
ATV (300mg)/RTV (100mg)	HDPE bottle 30 tablets	\$240	\$20.0	\$0.67				✓ ^{1,2}				
ATV (300mg)/RTV (100mg) + TDF/3TC (300/300mg)	2 HDPE bottle 30 tablets each of ATV/RTV + TDF/3TC	\$306	\$25.5	\$0.43				✓ ^{1,2}				
PEDIATRIC PRODUCTS												
ABC + 3TC (60mg/30mg) Dispersible	HDPE bottle 60 tablets	\$168	\$7.0			✓ ^{1,2}						
AZT + 3TC (60mg/30mg) Dispersible	HDPE bottle 60 tablets	\$72	\$3.0			✓ ²			✓ ¹			
AZT + 3TC + NVP (60mg/30mg/50mg) Dispersible	HDPE bottle 60 tablets	\$96.0	\$4.0			✓ ²		✓ ^{1,2}				
EFV (200mg) Scored	HDPE bottle 90 tablets	\$37.2	\$9.3							✓ ^{1,2}		

*Abbvie prices are currently applicable only to LDC (least developed countries) namely:

Afghanistan, Algeria, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Rep., Chad, Comoros, Congo-Brazzaville, Cote d'Ivoire, Dem. Rep. of Congo, Djibouti, East Timor, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Laos, Lesotho, Liberia, Libya, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, Sao Tome & Principe, Senegal, Seychelles, Sierra Leone, Solomon islands, Somalia, Sudan, South Sudan, Swaziland, Tanzania, Togo, Tunisia, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe



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GLOSSARY AND ABBREVIATIONS

3TC: Lamivudine; nucleoside analogue reverse transcriptase inhibitor.

ABC: Abacavir; nucleoside analogue reverse transcriptase inhibitor.

ANVISA: (Agência Nacional de Vigilância Sanitária), Brazilian National Health Surveillance Agency responsible for drug regulation in the country.

API: Active pharmaceutical ingredient.

ARIPO: African Regional Intellectual Property Organisation. There are currently 18 states which are party to the Lusaka Agreement and therefore members of ARIPO. These are: Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, Sierra Leone, Somalia, Sudan, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.

ATV: Atazanavir, protease inhibitor.

ATV/r: Atazanavir/ritonavir; boosted protease inhibitor.

AZT: Zidovudine (also abbreviated to ZDV), nucleoside analogue reverse transcriptase inhibitor.

Category 1: In this document, 'Category 1' (or 'Cat 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' (or 'Cat 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.

CD4: CD4 count measures the strength of the body's immunological response to HIV and thus the health of the immune system. CD4 testing is the most effective and widely used diagnostic tool used to decide whether and when to start HIV treatment.

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.

CIF: 'Cost Insurance and Freight'. A commercial term (incoterm 2010) 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 2010) 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.

COBI: Cobicistat; a drug currently in development used to increase the levels of elvitegravir and, possibly, HIV protease inhibitors, to allow for lower and fewer doses of these medications while maintaining effectiveness.

Compulsory licence (CL): A legally established mechanism that can be used to override a patent monopoly when a public health need is at stake. According to WTO, a CL is "when a government allows someone else to produce the patented product or process without the consent of the patent owner. It is one of the flexibilities on patent protection included in the WTO's agreement on intellectual property — the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement."

Co-pack: Several drugs packaged together, for example in a single blister, but in separate pills.

d4T: Stavudine; nucleoside analogue reverse transcriptase inhibitor.

Data exclusivity: The period during which the data of the original marketing authorisation holder relating to (pre-) clinical testing is protected. During this time, the generic applicant may not refer to the information of the original marketing authorisation holder before filing their applications for marketing authorisation.

ddl: Didanosine; nucleoside analogue reverse transcriptase inhibitor.

DDP: Delivery Duty Paid. A commercial term (incoterm 2010) meaning that the seller fulfils his obligation to deliver when the goods have been made available at the named place in the country of importation. The seller has to bear the risks and costs, including duties, taxes and other charges of delivering the goods to that point, cleared for importation. Whilst the EXW term represents the minimum obligation for the seller, DDP represents the maximum obligation.

DNDi: The Drugs for Neglected Diseases initiative, an independent, not-for-profit product development partnership, co-founded by MSF, working to research and develop new and improved treatments for neglected diseases, including paediatric HIV.

DRV: Darunavir, protease inhibitor.

DRV/r: Darunavir/ritonavir; boosted protease inhibitor.

DTG: Dolutegravir; new integrase inhibitor submitted for US FDA approval in 2013.

EC: Enteric-coated.

EFV: Efavirenz; non-nucleoside analogue reverse transcriptase inhibitor.

EMA: European Medicines Agency. Formerly European Agency for the Evaluation of Medicinal Products.

EML: Essential Medicines List. 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.

ERP: Expert Review Panel. Global Fund grant funds may only be used to procure medicines which are WHO-prequalified, authorised for use by a stringent drug regulatory authority (SRA), or recommended for use by an Expert Review Panel, composed of external technical experts who review the potential risks/benefits associated with the use of medicines that are not yet WHO-prequalified or SRA-authorised.

ETV: Etravirine; non-nucleoside reverse transcriptase inhibitor.

EU: European Union.

Evergreening: A common practice in the pharmaceutical industry whereby pharmaceutical companies seek to extend their patent monopolies on profitable medicines for as long as possible, by using the patent system to delay the entry of competitors into the market. To extend a patent, a company can, for example, change the medicine from a powder to a pill, or add another existing compound to the original compound if it has found it works better with this addition. These minor variations allow pharmaceutical companies to then make secondary applications for additional 20-year patents to extend their monopoly on the drug.

EVG: Elvitegravir; integrase inhibitor currently in development.

Ex-works (EXW): A commercial term (incoterm 2010) 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.

FCA: Free Carrier. A commercial term (incoterm 2010) meaning that the seller fulfils his obligation to deliver when he has handed over the goods, cleared for export, into the charge of the carrier named by the buyer at the named place or point. If no precise point is indicated by the buyer, the seller may choose within the place or range stipulated where the carrier shall take the goods into his charge. When, according to commercial practice, the seller's assistance is required in making the contract with the carrier (such as in rail or air transport) the seller may act at the buyer's risk and expense.

Continued overleaf ❖❖❖

❖ *Glossary and Abbreviations continued*

FDC: Fixed-dose combination – multiple drugs combined in a single pill.

FOB: 'Free on board'. A commercial (incoterm 2010) 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.

FTA: Free trade agreement.

FTC: Emtricitabine; nucleoside analogue reverse transcriptase inhibitor.

Generic: A generic drug is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference (originator) medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated. A generic company sells generic medicines.

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.

HBV: Hepatitis B virus.

IP: Intellectual property.

IRBM: Institute for Research in Molecular Biology.

LDC: UN classification of least-developed countries. There are currently 49 LDCs, 34 in Africa, 14 in Asia and 1 in the Caribbean.

LPV/r: lopinavir/ritonavir; boosted protease inhibitor.

MPP: Medicines Patent Pool. The Pool's mission is to bring down the prices of HIV medicines and facilitate development of better-adapted HIV medicines, such as simplified fixed-dose combinations and special formulations for children, by creating a pool of relevant patents for licensing to generic manufacturers and product development partnerships.

MSF: Médecins Sans Frontières (Doctors Without Borders), independent medical humanitarian organisation founded in 1971.

NGO: Non-Governmental Organisation.

NIH: National Institutes of Health.

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor.

Non-Assertion Covenant: A declaration of non-enforcement by a patent holder for its patent in stated territories. Immunity-from-suit is an agreement whereby the patent holder waives the right to sue, subject to prescribed terms and conditions.

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, Comoros, Congo, Côte d'Ivoire, Gabon, Guinea, Guinea-Bissau, Equatorial Guinea, Mali, Mauritania, Niger, Senegal, Togo.

Originator: An originator drug is a novel drug that was under patent protection when launched onto the market. An originator company is a company that sells originator medicines.

Patent: Patents are awarded to pharmaceutical companies when they develop a new drug. The patent grants that company the right to exclusively make, use and sell that drug for 20 years. It stops generic companies from making the drug and means the originator company can charge high prices without other companies undercutting them. The most effective and sustainable way to reduce the price of a drug is competition, but patents block other producers from entering the market.

Patent opposition: A mechanism that can be used to ensure that drug patents are not granted frivolously, whereby a person, non-governmental organisation (NGO), lawyer, health organisation, researcher or market competitor opposes a patent application, whether it has already been granted (post-grant opposition) or is still under analysis by a patent office (**pre-grant opposition**). Patent oppositions are a key way to protect public health interests.

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.

Prequalification: More commonly known as WHO Prequalification, the WHO List of Prequalified Medicinal Products was initiated by WHO and developed in collaboration with other UN 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.

Pro-drug: A pro-drug is a medication that is administered as an inactive (or less than fully active) chemical derivative that is subsequently converted to an active pharmacological agent in the body, often through normal metabolic processes. A pro-drug serves as a type of precursor to the intended drug.

Quad: A once-daily, single tablet regimen, containing TDF/FTC/COBI/EVG, and marketed by Gilead as Stribild.

R (or RTV): Low-dose ritonavir, used as a booster.

R&D: Research and development.

RAL: Raltegravir; integrase inhibitor.

RIL (or RPV): Rilpivirine, (TMC 278), Non-Nucleoside Reverse Transcriptase Inhibitor.

RTV: Ritonavir; protease inhibitor.

SQV: Saquinavir; protease inhibitor.

SRA: Stringent drug regulatory authority. A drug regulatory authority which is (a) a member of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, or ICH; or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein.

TAC: Treatment Action Campaign. Founded on 10 December 1998 in Cape Town, South Africa, TAC advocates for increased access to treatment, care and support services for people living with HIV and campaigns to reduce new HIV infections.

TAF: Tenofovir alafenamide; nucleotide reverse transcriptase inhibitor and pro-drug or precursor drug to tenofovir.

TDF: Tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

TTP: Trans-Pacific Partnership Agreement, a free trade agreement currently under negotiation between Australia, Brunei, Chile, Canada, Malaysia, Mexico, New Zealand, Peru, Singapore, the US and Vietnam, (with Japan in process).

TRIPS: Trade-related Aspects of Intellectual Property Rights.

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.

UNITAID: 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.

ViiV: Joint venture created in 2010 by GlaxoSmithKline, Pfizer and Shionogi focusing on the R&D and commercialisation of HIV medicines.

Viral load: HIV viral load measures the level of HIV in the blood. Effective HIV treatment should result in a very low (or 'undetectable') viral load.

VL: Voluntary licence.

WHO GPRM: WHO Global Price Reporting Mechanism.

WHO Prequalification: See Prequalification.

ZDV: Zidovudine (also abbreviated to AZT); nucleoside analogue reverse transcriptase inhibitor.

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