



UNTANGLING THE WEB OF

ANTIRETROVIRAL PRICE REDUCTIONS

15th Edition – July 2012

UNTANGLING THE WEB ONLINE!

Médecins Sans Frontières' guide to the prices of AIDS medicines is now in its 15th edition – and is also available in an online version. Stay up-to-date with the latest news on ARV prices and availability by checking:

 **utw.msfaccess.org**

NEW RESOURCE: PATENT OPPOSITION DATABASE

The Patent Opposition Database is an online space where civil society can share the resources and tools needed to oppose patents on medicine. Patents – which give a pharmaceutical company the right to make and sell a drug for 20 years without competition, and therefore charge high prices – create a barrier to accessing affordable medicines. The Database will gather contributions from around the world. It will allow 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, visit:

 **www.patentoppositions.org**



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BACKGROUND: ACCESS TO ANTIRETROVIRALS

Eight million people in developing countries are on HIV treatment today,¹ but the number of people who need access to HIV medicines is growing.

In June 2011, governments committed to a target of reaching 15 million people with antiretroviral treatment (ART) by 2015 at the UN High-level Meeting on HIV/AIDS.² If this target is met, UNAIDS estimates that up to twelve million infections and more than seven million deaths can be averted by 2020, and that the number of new infections could be reduced by more than half by 2015.³

Now is a critical time to ensure widest possible access to ART: a landmark scientific breakthrough in 2011 showed that treatment with antiretroviral medicines (ARVs) not only saves lives, but can also stop HIV from being transmitted by up to 96%.⁴ In response to this evidence, in 2012 the World Health Organization (WHO) issued guidance supporting immediate treatment—regardless of a person’s immune system’s status or CD4 count—for HIV-positive people who have HIV-negative partners, in order to help prevent transmission of the virus.⁵ At the same time, guidance was also issued suggesting the possibility of offering full antiretroviral therapy for life to all pregnant women living with HIV for prevention of mother-to-child transmission of the virus (PMTCT). This protocol—‘option B+’—is easier to manage than starting and stopping PMTCT⁶ with each pregnancy, and better for mothers and their babies.

It is therefore critical to ensure the most robust and easiest-to-use medicines needed are made affordable to the largest number of people in developing countries. Over the past year, since the last edition of *Untangling The Web*, there have been mild price reductions for the newer ARVs recommended by WHO in its 2010 guidelines for first-

Médecins Sans Frontières (MSF) began providing antiretroviral treatment (ART) for HIV/AIDS in 2000 in Thailand, Cameroon and South Africa, to a limited number of people living with HIV/AIDS in urgent need of treatment.

Today, MSF treats 220,000 people in 23 countries, and some MSF projects have been able to reach and maintain ‘universal access’ to treatment – defined as reaching 80% of the people in need for ART – in their districts.

The past twelve years have been rich in lessons learnt: how bringing treatment closer to where people live, to primary health centres and rural clinics, means more people can be reached with care; how simplified patient-friendly treatment, with several medicines combined into one pill, facilitates drug supply and adherence; how providing treatment for HIV and TB under the same roof and by the same health worker reduces the burden on patients; and how tasks can be shifted to overcome human resource shortages, so that nurses can be trained to perform many of

the duties previously reserved for doctors. But further strategies will be needed to get treatment to more people, sooner.

In several of our programmes, MSF has been looking at ways to make use of the latest scientific findings that HIV treatment is also HIV prevention. In South Africa, MSF is piloting an innovative approach to scaling up treatment dramatically to both save lives and reduce new HIV infections in the community. The pilot project in KwaZulu-Natal, the province hardest hit by HIV, seeks to demonstrate the feasibility of scaling up testing, providing treatment to people in an earlier stage of the disease’s progression, and increasing uptake of prevention methods. The aim is to reduce HIV and TB-related illness, as well as cut the number of new HIV infections.

For more on the tools, strategies and policies needed to get ahead of the wave of new infections, read MSF’s new report: *SPEED UP SCALE-UP: Strategies, Tools and Policies to Get the Best HIV Treatment to More People, Sooner.*

line therapy, like tenofovir. Greater reductions are needed to support further scale-up. Meanwhile, second- and third-line ARVs remain priced many times higher than first-line drugs.

Further, middle-income countries are no longer offered standardised price discounts by originator companies, forcing them to negotiate ARV price

reductions on a case-by-case basis. Some ground has been lost, as middle-income countries are once again paying exorbitant prices for the newest drugs. And battles over intellectual property in the world’s main producer of affordable ARVs—India—continue to heat up, while voluntary measures by companies to increase access require much closer scrutiny and investigation.

I. FIRST-LINE TREATMENT OPTIONS

NEW PRODUCERS ON HORIZON EXPECTED TO BRING FIRST-LINE PRICES DOWN

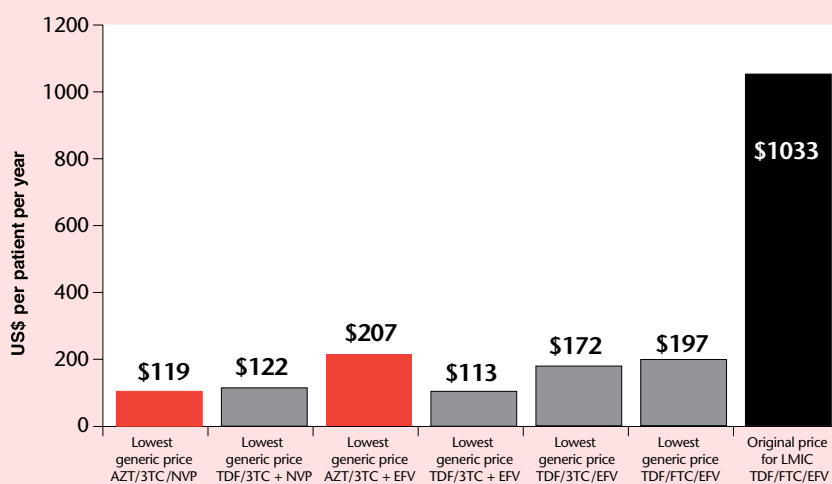
Providing people with well-tolerated medicines with few side-effects that make it easier to adhere to treatment is one of the key ingredients to successful HIV treatment outcomes. This helps delay the need to switch to much more expensive second-line regimens or beyond, because of resistance.

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

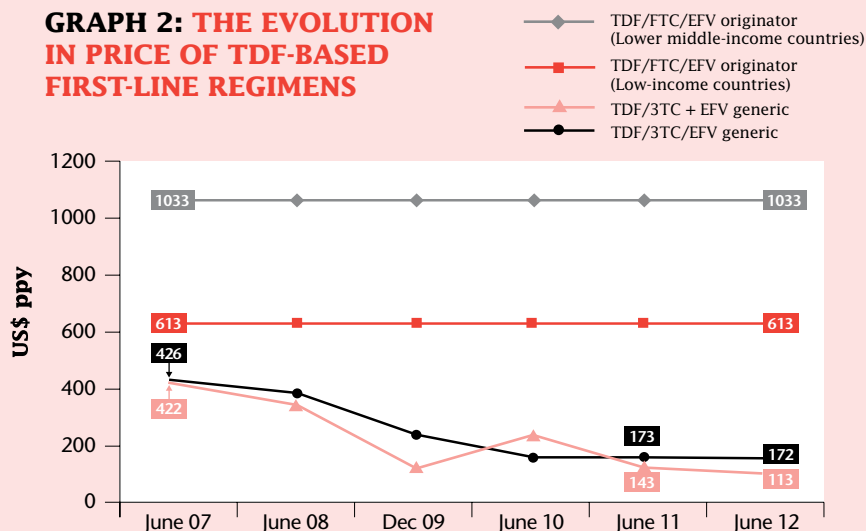
Many developing countries have begun to use either TDF or AZT for new patients starting treatment. In a survey of 16 countries where MSF works, all had removed d4T from their national protocol as the preferred first-line ARV, with eight having chosen TDF, five AZT and three choosing either of the two as the alternative.⁹

The higher cost of these alternatives to d4T has however slowed this switch. Tracking the price evolution of TDF- and AZT-based first-line regimens is therefore critical.

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



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



Graphs 1 and 2 chart the prices of different first-line regimens today, and their evolution over time. They reveal:

- ❖ That the price of TDF-based regimens is now nearly the same (when combined with nevirapine), or lower (when combined with efavirenz), than AZT-based regimens, for countries that can access generic versions because patents do not form a barrier, or where voluntary licences allow access to generic versions. The price of TDF-based first-line regimens has in fact been decreasing since 2007 for those countries.
- ❖ That for countries that are unable to access the generics because of patent barriers or because they are excluded from the scope of voluntary licences, the prices remain consistently high. The fixed-dose combination of TDF/FTC/EFV (produced by Merck/BMS/Gilead) – which is an adherence-friendly one pill a day – has remained priced at \$613 and \$1033 per patient per year (ppy) for lower-income and lower-middle-income countries, respectively, for the last five years. For middle-income countries, prices can be even higher, as most companies have eliminated their standardised discount programmes for these countries, in favour of case-by-case price negotiations.
- ❖ That where patents are not a barrier, countries can make use of therapeutically equivalent alternatives to TDF/FTC/EFV which are considerably more affordable. For the past three years, a WHO-prequalified once-a-day combination of tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) made by Matrix (Mylan) has been available. While its price has remained virtually static for the last year because it is the only product with WHO prequalification status, this is expected to change with new producers entering the market over the next year. This competition should help break Mylan’s monopoly on the market and bring prices down for this desirable combination. This in turn should help countries move away from d4T entirely.
- ❖ That until these new fixed-dose versions become available, the same regimen can also be procured and administered as two separate pills, to be taken once a day (a double fixed-dose combination of TDF/3TC plus EFV). The price of this co-pack has come down by 20% since last year, to \$113 ppy, making it the most affordable option of the WHO-recommended first-line regimens, with the added benefit of once-daily dosing.

In addition to being more affordable, TDF/3TC/EFV regimens have an advantage over AZT-based regimens thanks to their once-daily dosing (versus twice-daily for AZT) – see **table 1**. In addition, the latest WHO recommendations concerning EFV use during pregnancy are an additional incentive for countries to use this regimen – see **box**.

TABLE 1: FIRST-LINE REGIMENS – PILL BURDENS AT A GLANCE

The regimen of TDF, 3TC and EFV has the considerable benefit of once-daily dosing, and additional producers are expected to enter the market soon.

Regimen	Combination	Pills per day	Dosing
TDF with EFV	TDF/3TC/EFV	One	1 pill/once a day
TDF with EFV	TDF/3TC plus EFV	Two	2 pills/once a day
AZT with EFV	AZT/3TC plus EFV	Three	1 pill/twice a day + 1 pill/once a day
TDF with NVP	TDF/3TC plus NVP	Three	1 pill/once a day + 1 pill/twice a day
AZT with NVP	AZT/3TC/NVP	Two	1 pill/twice a day

NEW WHO ADVICE ON EFAVIRENZ USE DURING PREGNANCY

The World Health Organization recently issued new advice to countries highlighting the programmatic consequences of avoiding EFV use in pregnancy, and supporting its use as part of a simplified first-line treatment, including among pregnant women and those of reproductive age.¹¹

Efavirenz (EFV) had been recommended as the preferred option for a non-nucleoside reverse transcriptase inhibitor in

optimised first-line antiretroviral regimens since the 2010 WHO ART guidelines. However, there were persistent concerns about its safety in early pregnancy, resulting in increased frequency of regimen changes to less effective drugs, and increased complexity of treatment guidelines. Until recently, EFV was also considerably more expensive than its alternative, nevirapine (NVP). Recently, however, the cost of efavirenz has fallen considerably,

from \$185 ppy in 2007 to under \$50 ppy in 2012. In addition, an analysis led by MSF found that the evidence for suspecting that EFV is not safe in pregnancy is in fact very weak.¹⁰

This new WHO guidance provides more impetus for countries to choose the one-pill-a-day regimen of TDF/3TC/EFV as their preferred first-line regimen, and to use this regimen when starting all pregnant HIV-positive women on life-long ART (option B+).

II. SECOND-LINE TREATMENT AND BEYOND

IMPROVED OPTION FOR SECOND-LINE, BUT NEWER DRUGS REMAIN EXPENSIVE

IMPROVED OPTION FOR SECOND-LINE, BUT NEWER DRUGS REMAIN EXPENSIVE

With growing numbers of people in developing countries having been on treatment for a decade or even longer, ensuring the effectiveness of treatment, and long-term survival, depends on continuous access to newer and more potent ARVs. People need to switch to second-line regimens when they develop drug resistance over time.

In one of MSF's longest-running HIV/AIDS treatment programmes, in Khayelitsha, South Africa, 12.2% of patients on treatment for five years needed to switch to a second-line drug combination because of virological failure. Demand for second-line treatment is growing fast: it is estimated that almost half a million people will need second-line medicines by 2012.¹²

A key development for second-line therapy over the past year was the tentative approval granted by the US Food and Drug Administration (US FDA) of the first-ever FDC of atazanavir/ritonavir (ATV/r) in November 2011. This FDC finally provides an alternative boosted protease inhibitor to lopinavir/ritonavir (LPV/r).

ACCESSING VIRAL LOAD IN RESOURCE-LIMITED SETTINGS

The routine six-monthly measurement of viral load is a WHO-recommended diagnostic tool for monitoring all HIV-positive patients on ART.¹³ The use of routine viral load monitoring can trigger targeted adherence counselling and successfully diagnose treatment failure early enough to prevent the development of drug resistance.

Viral load testing is crucially important for deciding when it is necessary to switch a patient to more expensive second-line drugs. Unfortunately, due to the high cost

and complexity of the currently – available laboratory-based tests, viral load monitoring is not widely implemented in resource-limited settings. Treatment failure is therefore largely under-diagnosed.¹⁴

For more information on the need to implement viral load in resource-limited settings, and potential avenues to simplify tools and reduce their cost, read the new MSF report *UNDETECTABLE: How Viral Load Monitoring Can Improve HIV Treatment in Developing Countries*.



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Because of the improved dosing of ATV/r – just one pill, once a day, compared to LPV/r with two pills, twice a day – it will likely become more prominent in second-line therapy. It is also more affordable than the lowest reported price for LPV/r.

However, it is crucial that additional suppliers enter the market to ensure global supply does not rely solely on one manufacturer.

Today's most affordable second-line regimen (AZT/3TC + ATV/r) is priced at \$399 ppy, down from \$442 for last year's most affordable combination. This however is still three times more than the most affordable first-line

regimen. For countries where generic versions cannot be used because of patent barriers or because they are excluded from the geographical scope of the voluntary licences, the price can be many times higher.

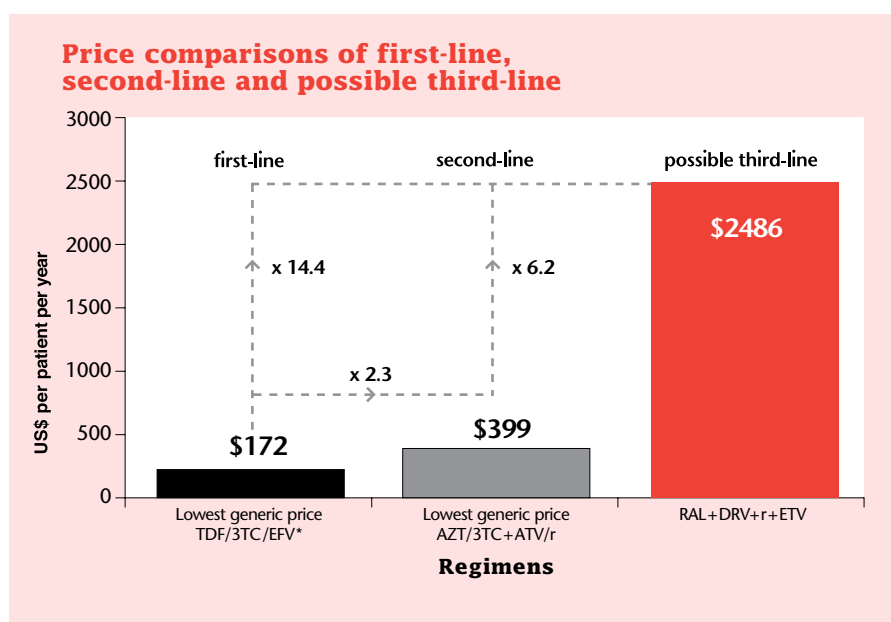
For people who need to be switched from second-line therapy, a possible regimen of raltegravir + darunavir + ritonavir + etravirine is priced at \$2,486 ppy at company discounted prices for sub-Saharan Africa and least-developed countries. This is over 14 times more than the most affordable first-line, and six times more than the most affordable second-line regimen (see graph 3).

GRAPH 3: DRAMATIC PRICE INCREASE FOR SWITCH TO SECOND- LINE ARV REGIMENS AND BEYOND

Changing a patient's regimen because of the emergence of resistance means relying on newer, patented, and therefore more expensive drugs. The price of a third-line regimen is over 14 times more than the most affordable first-line regimen, and over six times more than the most affordable second-line regimen. Patients and treatment providers are once again faced with the prospect of drugs being priced out of reach.

Newer ARVs remain prohibitively expensive, partially because demand for some of them is still small. This is unlikely to change since patents have prevented the broad and open generic competition that will drive prices down. This means that in middle-income countries, where companies no longer offer standardised price discounts and prices must be negotiated on a case-by-case basis, much higher prices are paid (see table 2). In Russia, which is classified by the World Bank as an upper middle-income country, raltegravir, darunavir and etravirine combined was procured at over \$27,000 ppy (see table 3). This does not even include ritonavir, which would be needed in addition to complete the regimen.

For those people already failing on their second-line combination, this unaffordable price will mean they almost certainly will be left without effective treatment options.



*While the price of the one-pill once-a-day FDC of TDF/3TC/EFV has remained virtually static at \$172 ppy because of the lack of competition from additional manufacturers, this combination also exists today as two separate products of TDF/3TC + EFV for \$113 ppy (see graph 1). In addition, with the imminent entrance of further manufacturers of TDF/3TC/EFV, price decreases are expected for the near future.

TABLE 2

Selection of prices paid in 2011 by countries for the newest ARVs, based on data from the Global Fund's Price and Quality Reporting database.¹⁵

Territory	Product	Unit Price in US\$	Price ppy in US\$
Cuba	darunavir 600mg tablet	9.60	7,008
West Bank and Gaza	darunavir 600mg tablet	7.23	5,276
Georgia	darunavir 300mg tablet	5.80	8,468
Côte d'Ivoire	darunavir 300mg tablet	0.84	1,233
Jamaica	darunavir 300mg tablet	4.50	6,570
Bulgaria	etravirine 100mg tablet	4.28	6,247
El Salvador	etravirine 100mg tablet	4.74	6,917
Burkina Faso	raltegravir 400mg tablet	1.52	1,108

TABLE 3

Prices paid in September 2010 by Russia for raltegravir, darunavir and etravirine.¹⁶

Product	Unit Price in US\$	Price ppy in US\$
raltegravir 400mg tablet	13.61	9,935
darunavir 600mg tablet	11.85	8,651
etravirine 100mg tablet	5.85	8,541
TOTAL		27,127

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LOOKING INTO THE PIPELINE: THE BEST TREATMENT OPTIONS TO SUPPORT SCALE-UP

Looking beyond today's options, MSF, with the support of experts, outlined a vision of how to make best use of the ARVs in the near and more distant future in resource-limited settings, given the need to decentralise and simplify care even further to support treatment scale-up.

There are promising new drugs for the treatment of HIV in the future, including new classes of drugs that have new ways of preventing the virus from replicating. Some have

the potential to be administered as long-acting formulations that would allow once-weekly or once-monthly dosing. Others could be potentially cheaper than the ARVs most commonly used today. And others still are currently used only for salvage therapy in developing countries – but already recommended for first-line therapy in some developed countries.

A meeting of experts on ARV sequencing¹⁷ convened by MSF

in September 2011, together with Esther (Ensemble pour une solidarité thérapeutique hospitalière en réseau) and SOLTHIS (Solidarité thérapeutique & initiatives contre le SIDA), considered the following regimens for resource-limited settings in the short-, medium- and long-term. But ensuring access to promising drugs in the development pipeline will require surmounting patent barriers that prevent access.

SHORT-TERM (ONE TO THREE YEARS)	
First-line ART	Adults + children over three years: TDF/3TC/EFV Children under three years: protease inhibitor-based regimen (current LPV/r syrup is unpalatable and requires refrigeration; a heat-stable sprinkle formulation could be ready in 2012)
Second-line ART	Protease inhibitor-based regimen, including ATV/r or DRV/r (both have lower pill burdens than LPV/r).
MEDIUM-TERM (THREE TO SIX YEARS)	
Treatment-naïve patients	TDF/3TC/EFV may still be preferable as first-line regimen. FDCs with newer drugs (e.g. the 'Quad', or rilpivirine-based combinations) should be assessed for potential comparative advantages over TDF/3TC/EFV in terms of price, tolerability, and applicability (in particular, use during pregnancy and use in TB co-infected patients) before adoption. Similarly, a potential protease inhibitor (PI)-based first-line with high genetic barrier to resistance could be preferable, on the condition that access to rifabutine-based FDC for TB treatment is assured, and sufficient data on safety during pregnancy is obtained. Once-daily ritonavir-boosted protease inhibitors (ATV/r or DRV/r) could in that case be options as first-line components.
Treatment-experienced patients	A DRV/r plus dolutegravir (DTG)-based regimen could prove to be a powerful second line, provided DTG continues to prove successful in trials for adults and children failing PI-based treatment.
LONG-TERM (TEN YEARS)	
	Long-acting formulations could revolutionise ART by simplifying prescribing, drug supply and pharmacy management. Rilpivirine (RIL), S/ GSK744 and DTG are in development as long-acting drugs, but combining these into a single long-acting formulation needs more attention. Further, new delivery systems such as patches, implants and injections that are under development could improve adherence. Additionally, nanotechnology currently being explored for RIL could enhance drug activity, improve toxicity profiles and reduce cost because less active ingredient is needed.

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TARGET CHARACTERISTICS OF FUTURE TREATMENT REGIMENS

Delivering ART at scale in resource-limited settings requires more than efficacious drugs; six additional key principles guide ART choice. **They are:**

Simplicity: Since high HIV-burden countries face a critical shortage of health workers, many countries have simplified HIV care to the point where it can be delivered by nurses at health centres. Keeping ART simple means prioritising FDCs, once-daily formulations, and regimens with minimal laboratory monitoring requirements.¹⁸

Tolerability: Side effects are a major driver of treatment interruption, drug substitution, and treatment discontinuation, all of which undermine treatment and prevention efforts.^{19, 20} In particular, providing ART as prevention implies giving ART to people who may not yet have experienced clinical illness and may therefore be more reluctant to adhere to drugs with side effects.

Durability: Regimens that have a high genetic barrier to resistance and include molecules with long half-lives will help reduce the risk of resistance associated with widespread, long-term ART delivery.

Heat stability: Temperatures in Africa regularly exceed 30°C, and access to refrigeration is often limited (especially in rural settings). Some second-line regimens with boosted protease inhibitors must be kept at 2–8°C, which is a significant constraint.

Universal applicability: Current regimens require frequent substitutions according to age, pregnancy, and interactions with other (non-HIV) drugs. The ideal

regimen would be safe and effective irrespective of disease stage, usable throughout pregnancy, could be given to both children and adults, and be taken together with drugs for common co-infections, notably tuberculosis.²¹ This would eliminate the need for these substitutions.

Affordability: Strategies that lower treatment costs should be prioritised; they include dose reduction, improved drug bioavailability, active pharmaceutical ingredient (API) cost reduction through improved chemistry process, and novel drug delivery systems and models of care. Strategies to remove barriers to generic competition should also be pursued.



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III. STEPS TO INCREASE AFFORDABILITY OF HIV MEDICINES

POLICIES TO BRING PRICES DOWN

Company-led discount programmes, based on the ‘differential prices’ that are mapped in this yearly report, have proven to be minimally effective at driving down the price of HIV medicines.²² It is the absence of patent barriers in key producing countries – or their removal – which enables generic competition to act as the main catalyst for lower prices.

Competition among multiple generic pharmaceutical manufacturers in countries where medicines were not patented, especially India, is what brought the cost of HIV/AIDS treatment down by 99% since 2000 (see graph 4).

The lack of pharmaceutical patents in India until 2005 additionally allowed for the production of FDCs, which both support patient adherence and are crucial to the simplification of treatment that has been central to global treatment scale-up. India has

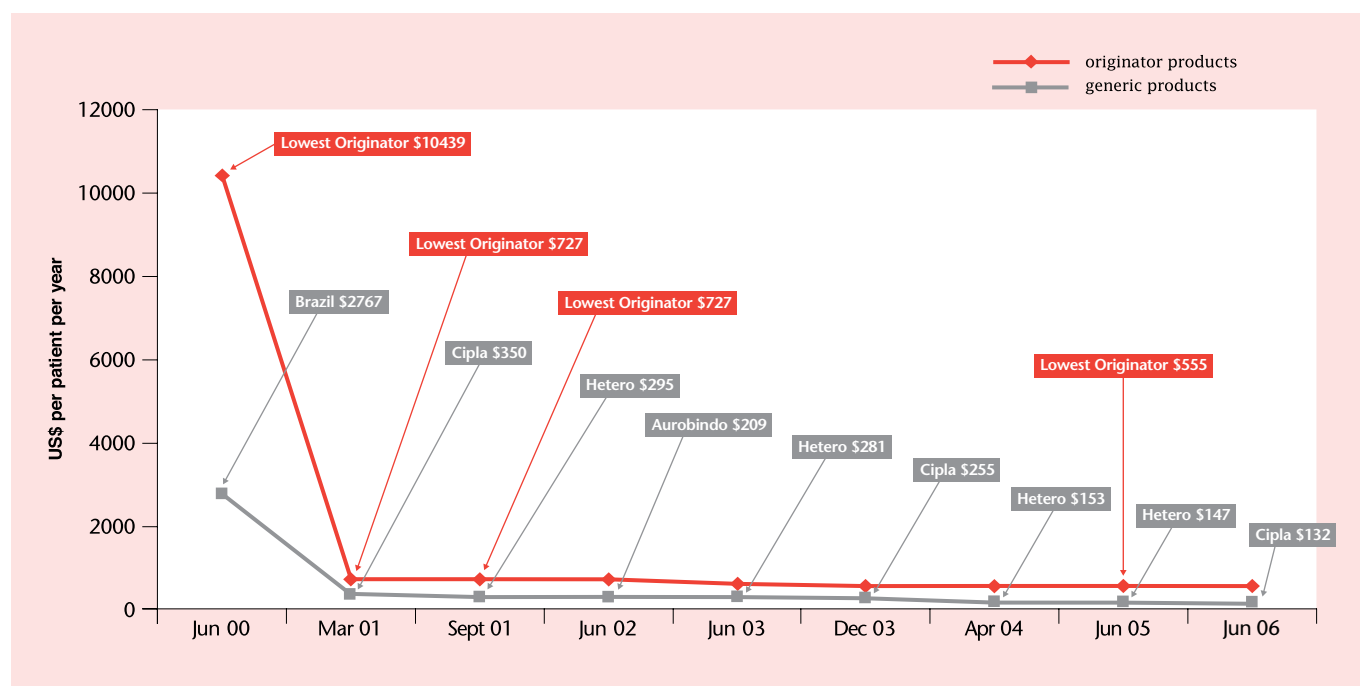
thus been called the ‘pharmacy of the developing world’: more than 80% of donor-funded purchases of ARVs for use in developing countries from 2003 to 2008 were manufactured in India, and more than 80% of the ARVs MSF uses are sourced from India.²³

GRAPH 4: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTIONS

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

The first-line combination of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), fell consistently from 2000 until 2006, when WHO first recommended a move away from

d4T-based treatment. The downward trend continued, to the extent that prices had fallen by 99% in ten years.



But increased drug patenting in key production countries, especially India, is starting to block price-busting generic competition for newer ARVs. If increased patenting and other intellectual property measures mean that generic competition cannot act as a catalyst to bring down the prices of medicines, tomorrow's battle for access to affordable ARVs will require more systematic use of compulsory licences and other policies to bring prices down, or through voluntary licensing arrangements that respond to public health needs.



COMPULSORY LICENCES: OPENING THE DOOR FOR LOWER PRICES

When drugs are patented, and pharmaceutical companies fail to make them available and affordable to patients in developing countries, governments can make use of their right, under international trade laws, to issue compulsory licences (CLs) to allow for open and broad generic competition. CLs are one of the public health safeguards enshrined in the TRIPS agreement,²⁴ which allow a government to override a patent by issuing a licence to a third party to produce or import a drug. CLs have proven to bring prices down dramatically by opening up the market to competition and thereby increasing access.

A number of CLs have been issued for ARVs in recent years, resulting in substantially lower prices for the medicines concerned. A compulsory

licence in 2007 in Thailand brought the price of lopinavir/ritonavir down by 75%; that same year Brazil overcame a patent on efavirenz, enabling the government to import a generic version from India at one third of the originator company price, and a compulsory licence in Ecuador in 2010 halved the cost of lopinavir/ritonavir to the public health system.

This year India issued its first CL – for the oncology drug sorafenib tosylate, marketed as Nexavar by Bayer – in March 2012, because the drug was considered unaffordable and had not been made available in sufficient quantities in the country.²⁵ The move will lead to a 97% price reduction for the drug. This sets an important precedent. In India, CLs can be issued when patented drugs are marketed

at an unaffordable price, as is the case for several of the newest ARVs, such as raltegravir and etravirine. This can potentially benefit not only Indian patients but also people in other countries if governments place orders with the generic manufacturer and so operationalise the CL provision for exports.

China too has lately adopted detailed procedural measures for the issuance of compulsory licences, in response to the potential need to use this flexibility to ensure access to medicines for the ongoing implementation of a universal healthcare programme, at a time when the country is unable to access more affordable versions of certain drugs as it is excluded from all recent voluntary licences (VLs).

VOLUNTARY LICENCES: READ THE FINE PRINT, IF IT'S PUBLIC

If they have the right terms and geographic reach, VLs can enable generic competition and allow for the sale of generic products in developing countries where patents are in force, improving the affordability and accessibility of medicines. In issuing a VL, a patent holder authorises a generic manufacturer to produce

and export a generic version of a medicine, often in exchange for royalty payments.

A number of ARVs are now being produced under different forms of licencing agreements between originator and generic producers. VLs with more than fifteen generic companies, primarily based in

India or South Africa, have already been agreed with pharmaceutical companies Merck, Bristol-Myers Squibb, ViiV, Johnson & Johnson and Gilead for 21 key second- and third-line ARV formulations, and more are under negotiation. **Annex 3** provides an overview of these different agreements.

Continued overleaf ❖

❖ *Voluntary licences: read the fine print, if it's public continued*

The claims as to the public health benefits of these VLs can not be verified, as the contractual terms and conditions are not public. A number of different concerns have emerged, however, from the little information that is publicly available:

- ❖ There is no VL that covers all developing countries, so VLs do not address the problem of affordability of medicines in excluded countries. Originator companies tend to design these agreements to strengthen their control over key developing country markets. Generic manufacturers are only allowed to sell their more affordable versions in a limited list of countries, usually least-developed countries and sub-Saharan Africa only. This leaves out lower middle and middle-income countries (with the notable exception of South Africa and India, which are often covered). VLs thereby often limit the number of countries that can benefit from the finished products, regularly excluding countries with sizeable populations of people living with HIV.
- ❖ Likewise, all VLs have restrictions on which countries or manufacturers can produce the finished product. This excludes other countries with generic production capacity and limits competition.
- ❖ There are other clauses in VLs that can limit the open competition that can bring prices down, such as the limits on which countries and which sources can be used to obtain active pharmaceutical ingredients (API). This is a harmful limitation as the API is the most expensive component of a medicine.
- ❖ VLs often contractually bar generic producers from supplying countries in which the originator company's patent applications are pending, leading to de facto monopolies – irrespective of whether a patent has been granted or not.
- ❖ Contractual restrictions on the supply to certain territories can also be used to block the use of a compulsory licence, as if a generic licensee were to supply excluded countries that had issued a CL, this would be a breach of the VL contract. Generic suppliers are therefore unlikely to take up the possibility of supplying to a country that had removed patent barriers through a CL, for fear that they would lose their VL contract if they fulfilled such a request.



There is one notable exception to this secrecy however. As an alternative to bilateral licencing, the Medicines Patent Pool (MPP), established in 2010, aims to develop voluntary licences transparently to manage patents collectively and in the interests of public health. The MPP could help overcome intellectual property barriers to facilitate the production for cheaper medicines, and allow the production of needed fixed-dose combinations that would otherwise require lengthy negotiations with numerous different patent holders, with an increasing impact if resulting licences cover all developing countries where patents are in force.

The MPP signed its first licencing agreement with a pharmaceutical

company, Gilead, in July 2011, covering four drugs – tenofovir, emtricitabine, cobicistat and elvitegravir – and combinations thereof. The licence slightly increases the geographic scope, from 95 to 112 territories, of an earlier licencing agreement on tenofovir signed bilaterally with generic companies and Gilead in 2006, but it continues to exclude key developing countries and restricts production to India.

However, there are a number of improvements. For example, the terms of the licence are public, allowing a full comprehension and public scrutiny of the conditions, which is an important step for transparency. It contains an explicit condition that the licence will

not block a licensee's right to supply countries excluded by the licence, should one of those countries issue a compulsory licence to override patents. The licence also provides a termination clause, so if the patents end up being rejected or not granted, a company that has signed the licence can terminate the agreement and freely manufacture the drug on its own.²⁶ This termination clause has already been used by two of the original 2006 licensees to terminate their licences on TDF.

Several VLs have been signed between originator companies and generic producers in parallel to the MPP; these bi-lateral deals have negotiated less favourable terms.



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WHAT POLICIES TO REIN IN DRUG COSTS?

Supporting policies that can ensure newer and better medicines are made affordable for people in developing countries is a political choice – one that countries have committed to at the UN since 2001 and re-iterated in the Declaration that concluded the 2011 UN High Level Meeting on HIV/AIDS.

❖ **Developing countries should make use of public health safeguards and other legal flexibilities to bring down the cost of medicines.**

Least-developed countries should use their right not to grant or enforce medicines patents until 2016, and the World Trade Organization should extend this deadline beyond 2016.

Governments should routinely exercise their right to override patents in the interest of public health by issuing **compulsory licences** to bring down drug costs.

Countries should design **flexible patent laws** that favour access to medicines. They should have **high standards for patentability** to ensure only innovative products are rewarded with patent monopolies. India's patent law for example contains key health safeguards, reserving monopoly status only for drugs that show a therapeutic benefit over existing ones. This prevents 'evergreening', a patent-extension strategy whereby a company makes a small change to a drug and receives a new 20-year patent. But this system is under

threat – this part of law is under attack by pharmaceutical company Novartis, whose ongoing case against the Indian government is scheduled to be heard in the country's Supreme Court in July 2012. A win for the company would likely lead to much broader patenting of drugs in India.

Patent oppositions are another crucial safeguard for access to medicines, so that undeserved patent applications can be challenged. India's law allows any interested party to oppose a patent both before it is granted (through a 'pre-grant' opposition), or after (through a 'post-grant' opposition). For more about patent oppositions, visit www.patentoppositions.org

Continued overleaf ❖

❖ What policies to rein in drug costs? continued

The use of these safeguards in the Indian law has resulted in the withdrawal of the patent applications on lamivudine/zidovudine and the rejection of key patent applications on tenofovir, darunavir, nevirapine syrup and lopinavir/ritonavir allowing generic companies in India to continue to manufacture, supply and export these HIV medicines to other developing countries.

In Brazil, the patent for lopinavir/ritonavir was annulled in February 2012 by the federal court of Rio de Janeiro, following an opposition filed by a manufacturer. This allowed for local production or importation of more affordable versions of a drug that the originator company Abbott was selling in Brazil for 47% more than the lowest global generic price. Oppositions have been filed on additional patents related to LPV/r.

South Africa provides an example of where introducing all key public health flexibilities into the patent law could help promote public health and ensure generic competition by preventing excessive patenting and evergreening. In 2008 alone, South Africa granted 2,442 pharmaceutical patents, compared to only 278 in Brazil for the five-year period from 2003 – 2008.²⁷ A stronger patentability criteria and patent examination system in Brazil account for this difference. The Treatment Action Campaign and MSF have called on South Africa to amend its patent law to include stricter patentability criteria, a patent review system, pre- and post-grant opposition, and an administrative rather than judicial process for granting compulsory licences, in the interest of public health.

Flexibilities that are proven to be ineffective should be reformed. World Trade Organization members should review and **reform the August 30 Decision**, designed to allow the exporting and importing of medicines under a compulsory

licence to countries which have no manufacturing capacity and cannot produce their own generic medicines.

The experience of the only use of this flexibility in Canada has shown that what was intended to be an ‘expeditious solution’ fails to meet the needs of developing countries with no or insufficient manufacturing capacity to import medicines patented in drug-producing countries.²⁸

❖ **Developed countries should refrain from pushing measures that impose even greater intellectual property protection than international trade rules require.**

A number of multilateral trade deals currently exceed the TRIPS agreement in their intellectual property protection requirements. The **Trans-Pacific Partnership Agreement** currently under negotiation between the US and Pacific Rim nations seeks to impose high levels of intellectual property protection that will limit access to medicines and could become a dangerous template for future agreements.

The European Union and the European Free Trade Association countries are currently pushing for policies to be included in **free trade agreements with India**, such as enforcement and investment provisions that will further restrain competition and impact access to affordable medicines.

By pushing drug prices up, such agreements also directly undermine efforts by US and European donor governments to finance and support treatment scale-up.

The US’s **Special 301 mechanism** is a further example of a bilateral punitive measure to challenge efforts by developing countries to ensure access to medicines for their populations, and to drive countries to implement intellectual property

measures into their domestic laws above those required by international trade law.

❖ **All countries should refrain from introducing IP enforcement measures that limit the production, export, transit and importation of generic medicines.**

Agreements and laws that conflate legitimate generic medicines with deliberately falsified medicines under the term ‘counterfeit’ should be avoided, reversed or rejected. The concerns over the effects on access to generic medicines of the **Anti-Counterfeiting Trade Agreement (ACTA)**,⁴⁵ for example, have led to the EU Parliament rejecting the treaty.

The harm such provisions can do was recognised in the decision of the Kenyan High Court in 2012 when it struck down, as a breach of the constitutional right to life, human dignity and health, three sections of the **Kenyan Anti-Counterfeiting Act 2008** that would have threatened access to generic medicines for people living with HIV. On going discussions at the East African Community level on anti-counterfeiting laws must ensure that similar provisions are not included.

The European Commission is currently reviewing the **EU customs regulations** that have in the past been used to detain generic medicines in transit through the EU on their way from one developing country to another. The proposed amendments tabled by the European Commission fail to ensure the smooth and free movement of legitimate generic drugs across trading routes and require further amendments.

❖ **All companies should make the terms of all voluntary licences public, and support mechanisms that encourage transparent, collectively managed and public-health focused licencing, by participating in the MPP rather than seek to create alternative approaches.**



TENOFIVIR FOR EVERYONE ON FIRST-LINE TREATMENT: A PERSPECTIVE FROM ZIMBABWE

Zimbabwe is moving ahead with its plans to start giving tenofovir to all patients on first-line antiretroviral treatment. The switch to tenofovir is happening in a phased manner due to financial limitations. Dr. Steven Van Den Broucke, who worked for MSF in the country from July 2010 to March 2012, explains the benefits for MSF and other health care providers of switching patients to tenofovir.

“We started to switch groups of patients who were initiated on stavudine to tenofovir last year, and now all patients are due to be switched to treatment with tenofovir by the end of this year.

A major reason for making the switch was that the drug is much easier to use in nurse-driven programmes. Using tenofovir in combination with efavirenz, for example, in a triple fixed-dose combination means it is possible now for us to initiate a patient on just one tablet, once a day, right from the very start of treatment. Also hugely beneficial is that fact that this combination of drugs—efavirenz, tenofovir and lamivudine—doesn’t interact with medicines the patient may be taking to treat tuberculosis at the same time.

The major problem with stavudine, which we are now replacing with tenofovir, has been the side effects it can produce in patients, such as lactic acidosis and peripheral neuropathy, both of which require careful medical monitoring.

Lactic acidosis is difficult to diagnose and while peripheral neuropathy can be spotted more easily, it is difficult to treat. And if it isn’t picked up early enough, the side effect becomes irreversible and can cause a lot of pain and prevent the patient from being able to walk. Both of these factors mean that it is much harder to manage a patient on stavudine than on tenofovir in a nurse-driven setting.

Also, because tenofovir causes fewer side effects in patients, it opens up the possibility, from a medical perspective, to increase the amount of time between patients’ clinic visits. Patients could in theory pick up a six-month supply of the drug when they visit the clinic, instead of the current usual three-month supply here. This would result in lower workload for programme staff. Since patient cohorts are always increasing, anything that can reduce workload within a programme is valuable.

After the green light from the national authorities, MSF started to provide

tenofovir in combination with efavirenz, instead of with nevirapine—it’s a preferable combination because it means patients only have to take one pill a day. But it is more expensive. We are currently providing this treatment ourselves in our projects, but hope to see the price of the combination drug drop within the next couple of years, allowing for a wider take-up across Zimbabwe, beyond MSF projects.”

“The benefits for patients are that if we use tenofovir with efavirenz in a triple fixed-dose combination tablet, people only need to take their medications once a day—usually in the evening—instead of taking medication twice a day which usually means once in the morning, once in the evening. This is the goal because it makes things much easier for patients to remember. Often they’ll talk about how on different days they have to leave home at different times in the mornings and sometimes these disruptions to their schedules mean missed dosages. So for them, one pill once a day is just one thing less to remember. There is substantial evidence that people do adhere to their medicines more when they only have to take them once a day. And better adherence to the first-line regimen is the key for long-term survival.”

Dr. MUSAED ABRAHAMS,
MSF HIV Training Coordinator,
Southern Africa Medical Unit



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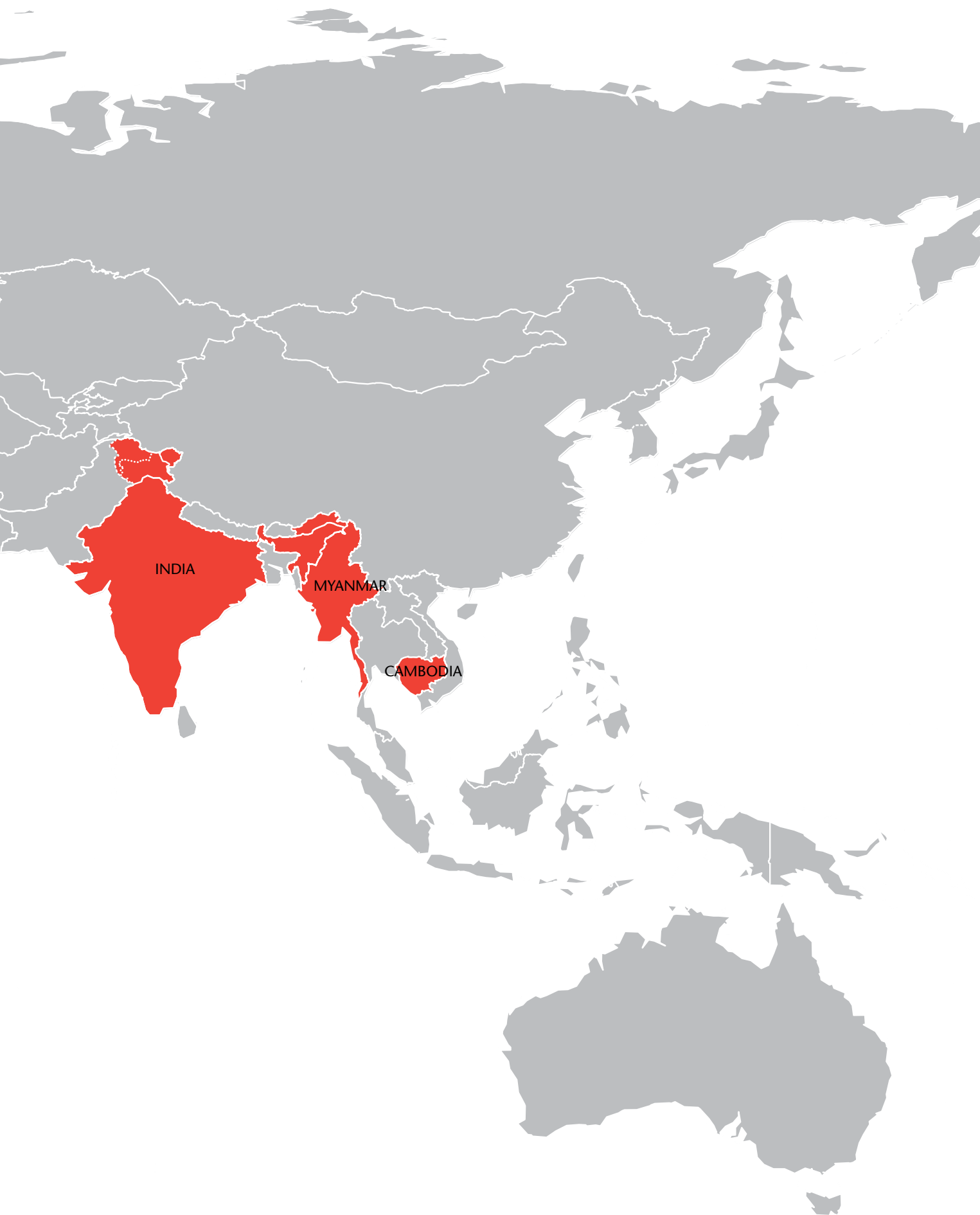
MSF HIV/AIDS TREATMENT PROGRAMMES

MSF PROVIDES ART TO 220,000 PEOPLE IN 23 COUNTRIES.



THE MSF ACCESS CAMPAIGN

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





QUALITY ISSUES

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

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

WHO PREQUALIFICATION

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

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

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 FOOD AND DRUG ADMINISTRATION

In May 2004, in support of the US President's Emergency Plan for AIDS Relief (PEPFAR), US FDA announced an initiative to help ensure that those being served by PEPFAR would receive safe, effective, and quality manufactured 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 or other exclusive rights in the US, tentatively approved products will be authorised for marketing in the country.

It should be noted that although the WHO prequalification system recognises the US FDA "tentative approval" scheme under PEPFAR, the inverse 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).⁹⁴

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 potentially 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.

But not all the products listed in this report have been quality-assured by WHO Prequalification or US FDA, and only some of them are used by MSF in its own projects. Products included in the List of Prequalified Medicinal Products (as of June 2012), 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 Prequalification¹⁰⁵ and the US FDA Approved and Tentatively Approved Antiretrovirals¹⁰⁶ for the latest list of prequalified products and for information on the status of dossier assessment.



METHODOLOGY

This report includes price information only for antiretrovirals (ARVs) that are recommended in WHO's latest ARV treatment guidelines or that have attributes that are favourable for use in resource-limited settings. This means that the following drugs have been removed from the list included in last year's publication: enfuvirtide, maraviroc, nelfinavir, rilpivirine and tipranavir. One exception is stavudine, which remains in the publication despite no longer being recommended by WHO, because it is still procured for use in many treatment programmes.

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 May 2012.

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 the 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 March 2012.

The company Macleods was invited to contribute to this publication, but chose not to provide price information.

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

- The information on prices given in this publication only relates to ARVs. It does not include other costs linked to antiretroviral treatment, such as diagnosis, monitoring or treatment of opportunistic infections.
- The manufacturers provide the prices listed in this publication. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower as a result of effective procurement procedures or negotiations. Therefore the document should not be viewed as a manufacturers' price list.
- Companies use different trade terms (known as incoterms). These trade terms outline the responsibilities of the manufacturer and purchasers with regard to transport, international freight and insurance costs. Additional information and definitions of incoterms can be found in the 'Abbreviations' section at the end of this guide. The incoterms of the prices provided by the companies are reported in **Annex 2**.
- Originator and some generic companies have different eligibility criteria for differential pricing for countries and entities, meaning not all countries and entities can access the price that is mentioned in this guide. The different categories of prices are detailed on the drug profile pages. More detailed information on the different eligibility criteria is provided in **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 40 different ARV formulations, both paediatric and adult. The current CHAI price list can be found in **Annex 6**.
- 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 is updated regularly, these 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 product 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.

The annual cost of treatment per patient per year (ppy) 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 then by 365. The price of the smallest unit is included in brackets.

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.

Within the tables, the information on the paediatric formulations is highlighted in light red in order to allow an easier distinction between adults and paediatric formulations.

QUALITY

Products quality-assured by the WHO Prequalification Programme or US FDA (as of June 2012) 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.

CATEGORIES 1 AND 2 ACCESS TO PRICE DISCOUNTS

Each originator company applies different eligibility criteria for its discounted ARV prices. 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. Companies often have two groups of countries that are eligible for their discounts, often called 'category 1' and 'category 2' countries, with category 1 including countries eligible for the deepest price discounts. Each company defines its own list of countries for categories 1 and 2. Please refer to **Annex 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**.

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

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

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

SPOTLIGHT ON ACCESS ISSUES – A LOOK AT PAEDIATRICS AND PATENTS

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 developing countries.

Two additional sections have been included to discuss and highlight specific issues with regard to **paediatrics** and **patents**.

CLINTON FOUNDATION PRICES

Some countries and programmes are eligible for further discounts through CHAI. The CHAI consortium list is found in **Annex 6**.



ABACAVIR (ABC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO Guidelines: Indicated for treatment for adults and adolescents. For infants and children, it is an alternate NRTI in first-line treatment.^{13, 29}
- 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 1998.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31, 32}
- World sales of originator product for 2011: Sales not reported; 2010: Sales not reported; 2009: US\$160 million; 2008: \$175 million; 2007: \$215 million; 2006: \$230 million; 2005: \$268 million; 2004: \$290 million.^{33, 34, 35, 36, 37, 38}
- Patents: GSK applied for the basic patents on ABC in 1989³⁸ and 1990,³⁹ 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 1995,⁴⁰ to the hemisulfate salt of ABC in 1998,⁴¹ and to compositions of ABC particularly relevant for paediatric use in 1999,⁴² which are due to expire in 2015, 2018 and 2019 respectively.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of June 2012) are in **bold**.

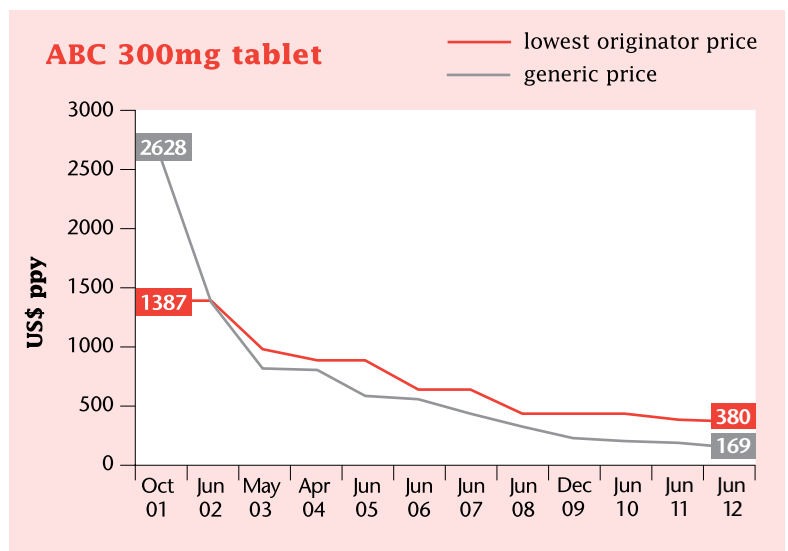
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy	Strides
ABC 20mg/ml oral solution (paediatrics)	12 ml	415 (0.095/ml)	183 (0.042/ml)	256 (0.058/ml)	210 (0.048/ml)	160 (0.036/ml)			
ABC 60mg tablet (paediatrics)	4			134 (0.092)	170 (0.117)		122 (0.083)		
ABC 300mg tablet	2	380 (0.520)		183 (0.250)	243 (0.333)	169 (0.232)	170 (0.233)	237 (0.325)	256 (0.350)

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

As of June 2012, there are six generic sources of ABC 300mg tablet which are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 73% while the generic price has dropped by 94%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

Affordability remains an issue with abacavir (ABC), despite the 94% decrease in price of the generic version since 2001. The current lowest generic price per patient per year for abacavir 300mg tablet is still more than double the lowest generic ppy of tenofovir (TDF) 300mg and zidovudine (AZT) 300mg.

Paediatrics

ABC is approved for use in children. In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ABC as one of the possible NRTIs to be given with lamivudine (3TC) and either an NNRTI or a PI in the first line. WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC and ABC preferred over stavudine (d4T).²⁹ ABC can also be part of a second-line regimen, depending on what has been used as first line.

There are currently three prequalified generic sources of the

ABC 60mg tablet. However, the price of this formulation is still high despite the fact that the lowest generic price has decreased from US\$134 ppy in 2011 to \$122 ppy in 2012. ABC 60mg is also combined in a paediatric FDC with 3TC 30mg tablet, the 2012 reported price for which is \$140 ppy. Please refer to the ABC/3TC drug profile.

Despite there being three qualified generic sources of the ABC 20mg/ml solution, price is still an issue. Currently, the lowest generic ppy for the abacavir solution is about double the lowest prequalified generic price ppy of the AZT 10mg/ml solution.

Patents

GSK could not apply for the basic patents on ABC in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement. The basic patents on ABC have now expired in China.⁴³

In addition, GSK applied for patents on the hemisulfate salt of ABC in India but withdrew this application

in October 2007 after it was opposed by civil society groups in a pre-grant opposition procedure.⁴⁴ However the same application on the hemisulfate salt of ABC was also filed by GSK in China in May 1998. It was granted in 2008 and will effectively block generic versions until 2018.

GSK also applied for a patent on the oral solution of ABC particularly relevant for paediatric use, which was granted in December 2007.⁴⁶ This patent raised concerns over the continued generic availability of the ABC paediatric formulation. However, the paediatric composition patent has not been used by GSK to block the development of the ABC/3TC FDC for children.

Two patents of ABC on the composition for paediatric use and the hemisulfate salt were granted in ARIPO countries, while a patent on the hemisulfate salt was granted in OAPI countries.⁴⁷



ATAZANAVIR (ATV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2010 WHO guidelines: Boosted ATV is indicated for second-line treatment for adults, adolescents and children above 15kg.^{13,29}
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approved by US Food and Drug Administration (FDA): June 2003.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$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.^{48,49,50,51,52,53,54}
- Patents: Novartis filed for the basic patent in April 1997 which is expected to expire in April 2017.⁵⁵ BMS is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998⁵⁶ and on the process for preparing the bisulfate salt and novel forms in 2005.⁵⁷

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 June 2012) are in **bold**.

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

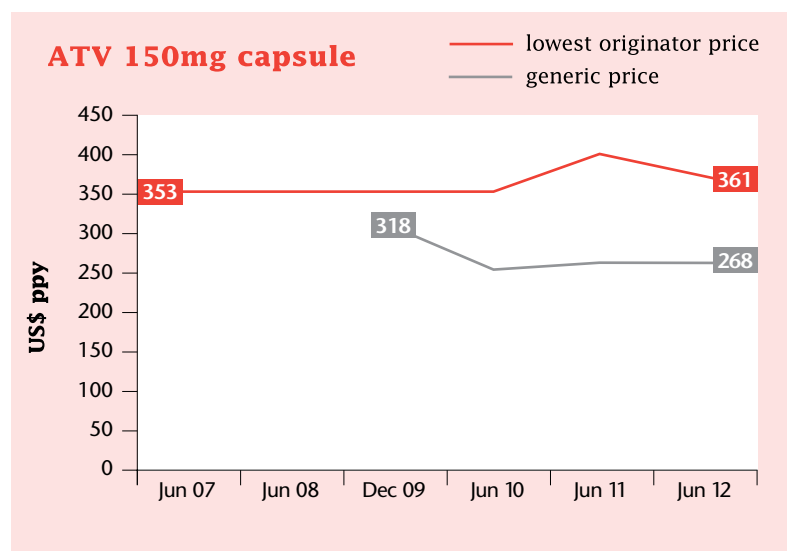
	Daily dose	Bristol-Myers Squibb		Emcure	Hetero	Matrix (Mylan)
		Category 1 countries	Category 2 countries			
ATV 100mg capsule	xx*			(0.267)		
ATV 150mg capsule	2*	412 (0.564)	361 (0.495)	268 (0.367)		
ATV 200mg capsule	xx*	(0.677)	(0.594)	(0.483)		
ATV 300mg capsule	1*			268 (0.733)	280 (0.767)	231 (0.633)

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

Evolution of the lowest price quoted for developing countries since 2009:

As of June 2012, there are two generic sources of ATV 150mg capsule quality-assured by US FDA or WHO prequalification but only one of the manufacturers of the prequalified generics provided pricing information for this publication.

Since 2011, the originator price has decreased by 12%. Since 2009, the generic price has decreased by 16%.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

Atazanavir (ATV) boosted with ritonavir (RTV) is one of two PIs recommended by WHO for second-line treatment, to be taken in combination with two NRTIs.¹³ Despite its importance for second line, there is currently only one WHO-prequalified or SRA-approved generic version of ATV 300mg capsule.

In November 2011, Matrix (Mylan) in India became the first manufacturer to have a US FDA tentatively approved source of boosted heat-stable ATV. Please refer to the ATV/r drug profile.

For patients co-infected with TB, ATV cannot be used with rifampicin so access to rifabutine needs to be secured, preferably in an FDC.

The prices provided for the generic version of the 100mg, 150mg, 200mg and 300mg capsules by Emcure did not differ from last year. The 300mg capsule by Matrix (Mylan) decreased by close to 8% in the past year.

Paediatrics

In March 2008, ATV was approved for use in children between six and 18 years of age by the US FDA.³⁰ It is indicated in the WHO treatment guidelines for infants and children above 15kg, although lopinavir/ritonavir (LPV/r) is the preferred boosted PI for second-line ART.²⁹

Patents

In most developing countries with generic pharmaceutical production capacity, including Brazil, China and India, Novartis and BMS filed patent applications related to the ATV compound,⁵⁸ bisulphate salt,⁵⁹ and the best route to making ATV⁶⁰ and its combination with other ARVs.^{61,62,63,64} 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 opposition⁶⁵ to Novartis's basic patent application⁶⁶ on the grounds of lack of novelty. The patent application has since been abandoned⁶⁷ but several divisional patent applications^{68,69} have been filed by Novartis.

In addition, a patent application was filed by BMS in 2006. It contained claims that covered the most efficient route of manufacturing ATV and its bisulphate salt.⁷⁰ This application was opposed by generic companies and the patent office recently rejected the application.⁷¹ However, BMS had already filed a divisional patent application⁷² which has been opposed by Cipla. These divisional and other patent applications on ATV and its use in combination with other ARVs^{73,74,75,76} warrant additional pre-grant oppositions.⁷⁷ Abbott has filed patent applications on RTV in India and other developing countries which, if granted, will block the development of and access to generic ATV/r FDCs.

In February 2006, BMS granted technology transfer and voluntary licences to two generic manufacturers (Emcure and Aspen) to manufacture and sell ATV. In February 2008, Emcure received US FDA tentative approval for the 100mg, 150mg and 200mg ATV capsules. Under the terms of the licences, however, sales of these products are royalty-free but are restricted to sub-Saharan Africa. BMS has a separate agreement with Emcure that covers India.⁷⁸ Licencing agreements in India should not be necessary if patent oppositions are successful. If patents are granted, India and other countries could issue compulsory licences to enable unrestricted competition from generic manufacturers, in order to bring prices down, increase access and

facilitate the development of an ATV/r FDC. In June 2011, BMS signed an immunity-from-suit agreement with Matrix (Mylan) Laboratories enabling the generic company to manufacture and sell ATV in sub-Saharan Africa and India.⁷⁹ 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 impossible.

BMS' differential pricing structure is limited to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries such as Brazil paying more than \$1,000 ppy, a prohibitive price for many of these countries.⁸⁰

In Brazil, BMS' monopoly led to shortages of ATV in 2005⁸¹ and 2011⁸² and several patients had to change treatment regimens. Civil society groups then urged the government to issue a compulsory licence (CL) arguing Brazilian law justified the measure.⁸³ After the second shortage however, the government announced the creation of a public-private partnership for the local production of ATV,⁸⁴ preferring to negotiate with BMS rather than issue a CL to stimulate the local production of more affordable generic versions. The reasons for this choice remain unclear and civil society groups continue to demand transparency over the contractual terms and conditions of this agreement, particularly since it involves a publicly-owned laboratory. To date, no information concerning price reductions or sale restrictions for this product has been made available. In 2011, a year's treatment using the 300mg tablet in Brazil cost \$1,022. By April 2011, around 40,450 patients in Brazil were taking ATV as part of their treatment regimen.⁸⁵

For details on voluntary licences including the BMS/Emcure/Aspen and the BMS/Brazil agreements, see Annex 3.



ATAZANAVIR/ RITONAVIR (ATV/r)

GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- 2010 WHO guidelines: Indicated for second-line treatment for adults, adolescents and children.^{13,29}
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): November 2011 (tentative approval scheme), for Matrix (Mylan) product.⁸⁶
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults and the 3rd edition for children.^{31,32}

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 June 2012) 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	Matrix (Mylan)
ATV/r 300/100mg tablet	1	304 (0.833)

Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

Atazanavir (ATV) boosted with ritonavir (RTV) is one of two PIs recommended by WHO for second-line treatment, to be taken in combination with two NRTIs.¹³ In November 2011, a first generic source of this product was WHO-prequalified.

The introduction of this heat-stable formulation represents a step forward for access to second-line ARVs, as it represents the first FDC alternative to heat-stable lopinavir/ritonavir (LPV/r), currently the most commonly used protease inhibitor. This FDC has the added benefit of reducing the pill burden for patients – down from four pills a day for heat-stable LPV/r to one pill a day for ATV/r.

Besides, the quoted price of US\$307 ppy is lower than the lowest reported price of the LPV/r heat-stable formulation, which stands at \$368 ppy. However, there is a need for additional sources

to ensure that the global supply of this product does not rely on only one manufacturer. Additional manufacturers could mitigate the impact of any constraints in terms of eligible countries for procurement.

For patients co-infected with TB, ATV cannot be used with rifampicin so access to rifabutin needs to be secured, preferably in an FDC.

Paediatrics

In March 2008, ATV was approved for use in children between six and 18 years of age by the US FDA.³⁰ ATV boosted with RTV is indicated in the WHO treatment guidelines for infants and children above 15kg, although LPV/r is the preferred boosted PI for second-line ART.²⁹

There are currently no generic prequalified sources of the paediatric FDC.

Patents

A patent application on ATV/r is pending in India.⁸⁷

In June 2011, BMS signed an immunity-from-suit agreement with Matrix (Mylan) enabling the generic company to manufacture and sell ATV in sub-Saharan Africa and India.⁸⁸ Like other voluntary licences, full terms and conditions of this agreement are not known to evaluate its actual impact on access and price competition. Moreover, this agreement only covers a limited number of countries and patents may create access barriers in other countries.

For details on voluntary licences, see Annex 3.

Please refer to the individual drug profiles of ATV and RTV for further details.



DARUNAVIR (DRV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2010 WHO Guidelines: Boosted DRV is listed as a potential third-line treatment for adults, adolescents and children above six years of age.^{13,29}
- Originator company and product brand name: Janssen Therapeutics, formerly known as Tibotec (a subsidiary of Johnson & Johnson), Prezista.
- First approved by the US Food and Drug Administration (FDA): June 2006.³⁰
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition for adults or the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$1.2 billion; 2010: More than \$1 billion reported.^{89,90}
- Patents: The basic patent was applied for by Searle and Monsanto in August 1993⁹¹ and is due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to DRV in 1999⁹² and licenced them to Tibotec for development.⁹³ 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 2025.⁴⁷

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 June 2012) 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)	Hetero
DRV 300mg tablet	4**	803 (0.550)	
DRV 400mg tablet	2*		730 (1.000)
DRV 600mg tablet	2**		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.

Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

The 2010 WHO guidelines for adults and adolescents recommend boosted darunavir (DRV) together with etravirine (ETV) and raltegravir (RAL) as the treatment option for patients failing second-line ART.¹³

DRV requires boosting with ritonavir (RTV) – there are currently no FDCs combining the two drugs.

The price reported by Janssen (J&J) for sub-Saharan Africa and least developed countries outside of Africa has decreased for DRV 300mg tablet from US\$1095 ppy to \$803 ppy (27%).

Janssen (J&J) has indicated that the DRV 600mg tablet is in the process of being registered in sub-Saharan Africa and will eventually replace the 300mg tablet formulation over time – the discount price offered by the company is expected to remain unchanged.

Although no price information was provided for this edition of *Untangling The Web*, Cipla produces a generic version of DRV, currently only available for the Indian market.

On May 31, 2012, Hetero's 400mg and 600mg Darunavir tablets were Global Fund Expert Review Panel (ERP) approved, making this the first third-line generic ARV product available as an option for donor driven procurement. The Global Fund ERP is a temporary approval for pharmaceutical products, while awaiting prequalification by the WHO or a Stringent Drug Regulatory Authority. The ERP's approval is valid for no more than a period of 12 months. The list of countries eligible for these prices have not been disclosed.

Paediatrics

According to 2010 WHO treatment guidelines for infants and children, RAL and DRV may be used for older children as part of a third-line regimen.²⁹

In December 2011, DRV was approved for use in children between three and 18 years of age. Paediatric formulations exist as 100mg/ml oral suspension and 75mg and 150mg tablets.⁹⁵

As with all protease inhibitors, DRV must be given with an RTV booster – however the only currently available paediatric formulation of the 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 an FDC 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.²⁹

Patents

The basic patents related to DRV⁹⁶ could not be applied for in India as the country did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement. Janssen (J&J) has nevertheless applied for several patents in India related to the pseudo-polymorphic form,⁹⁷ the method for preparation of key intermediates of DRV⁹⁸ and combinations with RTV⁹⁹ and with both tenofovir (TDF) and RTV.¹⁰⁰ The Indian patent office has rejected several applications – related to pseudo-polymorph,¹⁰¹ the method for preparation of key intermediates and the combination of DRV with RTV.¹⁰² Other applications have been opposed by generic manufacturers – the patent application on the combination of DRV with TDF was withdrawn after opposition.¹⁰³

The patent threat to the combination of DRV with RTV nevertheless continues as Janssen (J&J) filed a divisional application¹⁰⁴ at the Indian patent office, along with appeals to the rejections. In addition, Abbott has filed patent applications on RTV in India and other developing countries which are pending – if granted, these would block the development of and access to generic DRV/r FDCs.

In China, Janssen (J&J)⁴³ 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.⁴³ Four DRV-related patents have been granted in South Africa.⁴⁷ 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 a mechanism designed to boost access to more affordable HIV drugs in the developing world. 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 darunavir in all developing countries, however, because additional patents are held by Janssen (J&J). In December 2011, Johnson & Johnson – which acquired Tibotec in 2002 – announced its decision not to enter into negotiations with the Pool,¹⁰⁸ and that it would not be licencing its HIV drugs portfolio, including DRV, to the Pool.¹⁰⁸ In doing so, J&J has effectively made the NIH licence useless for manufacture and export to countries where J&J has a patent.

J&J is however engaging in voluntary licencing with two generic companies – Aspen in South Africa and Emcure in India¹⁰⁹ (but only for packaging and distribution). The terms of the licence are not public. In addition, the geographical scope is limited – the agreements with Aspen and Emcure exclude many low- and middle-income developing countries, for which the price can be over \$13,100 ppy. With the patent restrictions in place, robust generic competition will not be possible until J&J is ready to consider more open and transparent licencing mechanisms. See Annex 3.

In June 2011, J&J announced that it had entered into a licence agreement with Gilead for the development and commercialisation of a new once-daily single tablet FDC containing DRV and Gilead's cobicistat. Subject to regulatory approval, J&J will be responsible for the formulation, manufacturing, registration, distribution and commercialisation of the DRV/cobicistat FDC 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.



DIDANOSINE (ddl)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO guidelines: Indicated as an alternative second-line therapy for children and infants.²⁹
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Videx/Videx EC.
- First approved by US Food and Drug Administration (FDA): October 1991 for chewable tablets; October 2000 for enteric-coated capsules.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- 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.¹¹¹
- Patents: Although the basic patent on ddl filed in 1985 by the National Institute of Health (NIH), a US government research institute, has expired, BMS holds patents on improved formulations in some countries which run until 2012 and 2018.¹¹²

PRICE INFORMATION

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

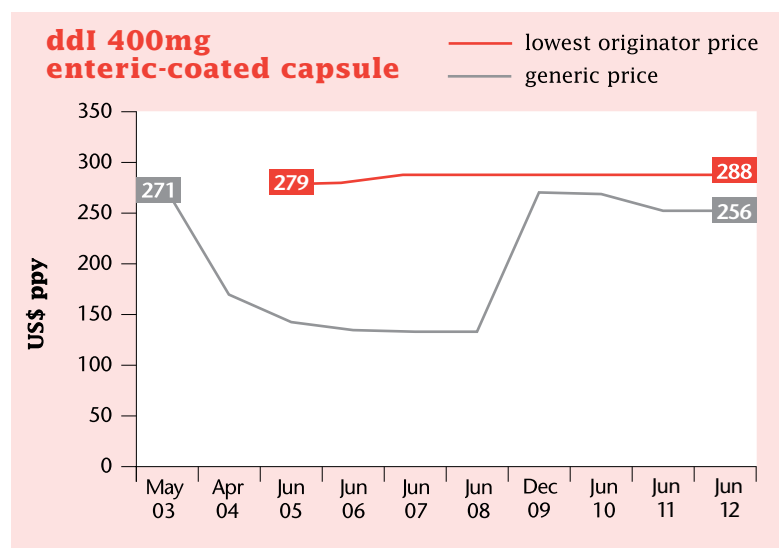
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of June 2012) are in **bold**.

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

	Daily dose	Bristol-Myers Squibb		Aurobindo	Matrix (Mylan)	Ranbaxy
		Category 1 countries	Category 2 countries			
ddl 2g powder for reconstitution (final concentration 10mg/ml) (paediatrics)	12ml	233 (12.590/2g)	Case-by-case basis			
ddl 25mg tablet (paediatrics)	6	256 (0.117)	Case-by-case basis			402 (0.183)
ddl 50mg tablet (paediatrics)	xx	(0.158)	Case-by-case basis			(0.217)
ddl 100mg tablet (paediatrics)	xx	(0.213)	Case-by-case basis	(0.133)		(0.250)
ddl 150mg tablet (paediatrics)	xx			(0.200)		
ddl 200mg tablet (paediatrics)	xx			(0.258)		
ddl 125mg enteric-coated capsule (paediatrics)	1			110 (0.300)	119 (0.325)	
ddl 200mg enteric-coated capsule	xx			(0.400)	(0.471)	
ddl 250mg enteric-coated capsule	1	223 (0.611)	277 (0.758)	170 (0.467)	180 (0.492)	(0.484)
ddl 400mg enteric-coated capsule	1	288 (0.789)	357 (0.978)	256 (0.700)	267 (0.733)	243 (0.665)

Continued overleaf

❖ *Didanosine (ddl) continued*



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

As of June 2012, there are two generic sources of ddl 400mg enteric-coated capsule quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2005, the originator price has increased by 3%. Since 2003, the generic price has decreased by 5%.

SPOTLIGHT ON ACCESS ISSUES

There are very few WHO-prequalified generic sources of the didanosine (ddl) enteric-coated capsules, and even fewer for the lower strength and non-enteric-coated formulations which are included in the WHO paediatric guidelines and indicated as an alternative second-line treatment for children and infants.

Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ddl to be given as part of second-line treatment, depending on what has been used as a first line.²⁹ In spite of this recommendation, there are very few WHO-prequalified generic sources of the lower-strength formulations and the suspension.

The paediatric formulations for younger children are buffered tablets that come with a high pill burden, or a ddl powder for reconstitution which requires multiple dilutions, first with water and then with an antacid to obtain the final concentration. Once reconstituted, the solution must be refrigerated and kept for a maximum of 30 days.

For older children who can swallow, the best adapted option is the ddl enteric-coated 125mg capsule. However, Bristol-Myers Squibb (BMS) did not provide price information for this specific product.

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 countries⁴⁷ – the importation of the more affordable version from India is blocked.

In Brazil, the active ingredient is in the public domain which has allowed the Government to locally produce the generic version as a powder for oral solution.¹¹³ However, the enteric-coated capsule remains under patent protection.

In June 2011, BMS signed an immunity-from-suit agreement with Matrix (Mylan) enabling the generic company to manufacture and sell ddl only in sub-Saharan Africa and India.¹¹⁴ For details on voluntary licences including the BMS/Matrix agreements, see Annex 3.



EFAVIRENZ (EFV)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2010 WHO Guidelines: Indicated, in combination with other antiretrovirals, for first- and second-line treatment for adults, adolescents and children above three years of age.^{13,29} EFV cannot be used in infants below three years.²⁹
- Originator companies and product brand names: Bristol-Myers Squibb (BMS), Sustiva; or Merck, Stocrin.
- First approved by US Food and Drug Administration (FDA): September 1998.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$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; and 2003: \$544 million.^{48,49,50,51,115,116,117}
- Patents: The basic patent on EFV was filed by Merck in 1993 and is due to expire in 2013.¹¹⁸ Subsequently, Merck filed for patent applications related to crystallised forms, due to expire in 2018.¹¹⁹

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 June 2012) are in **bold**.

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

	Daily dose	Merck		Aspen	Aurobindo	Cipla	Emcure	Hetero	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Strides
		Category 1 countries	Category 2 countries										
EFV 30mg/ml suspension (paediatrics)	xx	(0.094/ml)	Case-by-case basis										
EFV 50mg capsule (paediatrics)	xx				(0.082)					(0.072)			
EFV 50mg tablet (paediatrics)	xx	(0.120)	Case-by-case basis										
EFV 100mg dispersible tablet (paediatrics)	xx											(0.150)	
EFV 200mg capsule	3				91 (0.083)	146 (0.133)				61 (0.056)		82 (0.075)	
EFV 200mg tablet	3	394 (0.360)											113 (0.103)
EFV 600mg tablet	1	237 (0.650)		62 (0.170)	61 (0.167)	66 (0.180)	61 (0.167)	53 (0.145)	49 (0.133)	44 (0.120)	97 (0.265)	56 (0.153)	46 (0.125)

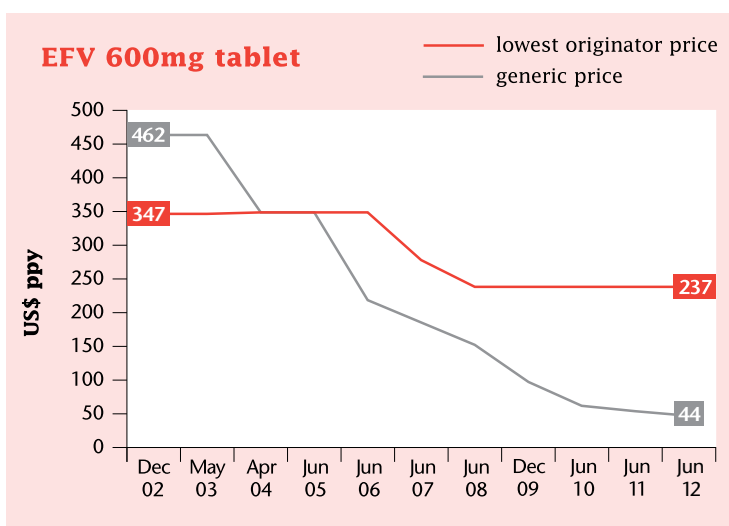
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❖ Efavirenz (EFV) continued

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

As of June 2012, 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% while the generic price has dropped by more than 90%.



SPOTLIGHT ON ACCESS ISSUES

Efavirenz (EFV) is a key drug for first-line treatment, in combination with lamivudine (3TC) or emtricitabine (FTC) and tenofovir (TDF) or zidovudine (AZT). It is recommended as the preferred NNRTI for patients starting ART while on tuberculosis treatment.¹³ This fact is illustrated by the presence of nine WHO-prequalified generic sources, with the lowest price at US\$44 for the 600mg tablet. Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as part of a simplified first-line treatment including among pregnant women and those of reproductive age.

Paediatrics

There is still no established dosing of EFV for children younger than three years of age based on WHO treatment guidelines for infants and children.²⁹ There is an urgent need to establish the dosing of EFV for this age group. In the absence of such data, treatment options for children remain limited, particularly for HIV/TB co-infected young children who cannot be given nevirapine (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 by Merck only. There are WHO-prequalified sources for the 50mg tablets and capsules, the 100mg capsules and the 100mg dispersible tablets.

The generic prices of the paediatric formulations are stable, with the exception one of the generic 50mg capsules, whose price rose by 34% in the past year- from \$0.047 per capsule in 2011 to \$0.072 per capsule in 2012 – after the product secured WHO prequalification.

Patents

Merck does not hold a product patent for EFV in India. However, Gilead¹²⁰ filed a patent application related to a combination of EFV with other ARVs – the crucial once-a-day pill with tenofovir and emtricitabine (TDF/FTC/EFV). In India, the patent office has already rejected Gilead's application,¹²¹ as combinations of known medicines are not patentable under its patent law. However the threat remains as Gilead has already filed several divisional applications – one of which is still pending examination.¹²²

BMS and Gilead filed for a patent once again for the once-a-day pill TDF/FTC/EFV¹²³ which could impact access to improved first-line ARV treatment in the developing world. In 2010, Cipla filed a pre-grant patent opposition to this patent application which is under examination in India.

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.^{124, 125}
- In May 2007, Brazil – after numerous unsuccessful negotiations with Merck – issued a compulsory licence to import more affordable generic versions of EFV from India. At the time, the price of EFV in Brazil was \$580 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a WHO-prequalified generic version for \$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched the national generic version of EFV for use in the Brazilian health system.¹²⁶
- 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 licence 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.¹²⁷



EMTRICITABINE (FTC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO guidelines: Indicated for first- and second-line treatment for adults and children, especially for adolescents over 12 years of age with hepatitis B.^{13,29}
- Originator company and product brand name: Gilead, Emtriva.
- First approved by US Food and Drug Administration (FDA): July 2003.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$29 million; 2010: \$28 million; 2009: \$28 million; 2008: \$31 million; 2007: \$32 million; 2006: \$36 million; 2005: \$47 million; 2004: \$58 million.^{128,129,130,131,132,133}
- 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.^{134,135} Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.^{136,137} These are due to expire between 2010 and 2012.

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 June 2012) 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
FTC 200mg capsule	1	58 (0.158)	85 (0.233)

SPOTLIGHT ON ACCESS ISSUES

According to the WHO treatment guidelines, FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related, shares the same efficacy against HIV and hepatitis B, and has the same resistance profile.^{13,29}

WHO treatment guidelines for adults and adolescents recommend 3TC or FTC, to be used in combination with zidovudine (AZT) or tenofovir (TDF) and an NNRTI, such as efavirenz (EFV) or nevirapine (NVP), as a first-line treatment regimen.^{13,29}

Paediatrics

FTC or 3TC needs to be used in conjunction with other NRTIs and NNRTIs in children, according to WHO treatment guidelines for infants and children.²⁹

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

FTC. Paediatric FDCs containing lamivudine do exist however – please refer to the relevant drug profiles.

Patents

In 2005, Gilead acquired the royalty interest for FTC under a \$525 million agreement with Emory University.¹³⁹

Although 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 reported holding patent rights on FTC in 45 other developing countries.¹³⁸

In mid-2006, Gilead signed licencing agreements with generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's TDF in combination with other ARVs, including FTC,

to a limited list of countries – in return for the payment of a five per cent royalty.¹⁴⁰ In July 2011, Gilead 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.

The geographical scope conditions of the two licences differ. Gilead's 2006 licence covers 95 territories, whereas the 2011 licence covers 112 territories. Out of these 112 countries, FTC patents are granted or filed in 45 developing countries. The MPP licence contains a covenant not to enforce FTC patents and allows 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).
- 2010 WHO Guidelines: Indicated for potential third-line treatment for adults.¹³
- Originator company and product brand name: Janssen Therapeutics, formerly known as Tibotec (a subsidiary of Johnson & Johnson), Intelence.
- First approved by the US FDA: January 2008.³⁰
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition for adults or the 3rd edition for children.^{31,32}
- World sales of originator product: Sales are not reported in the company's annual report.
- Patents: The basic patent on etravirine was applied for by Janssen Pharmaceuticals in 1999 and is due to expire in 2019.¹⁴¹ 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 June 2012) 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)
ETV 100mg tablet	4	438 (0.300)

SPOTLIGHT ON ACCESS ISSUES

The 2010 WHO guidelines for adults and adolescents recommend boosted darunavir (DRV), together with etravirine (ETV) and raltegravir (RAL) as the treatment option for patients failing second-line ART regimens.¹³

The price of the ETV 100mg tablet decreased from US\$913 ppy last year to \$438 this year. There is no generic source for this product.

Paediatrics

The 2010 WHO treatment guidelines for infants and children state that ETV is indicated for use in treatment-experienced children above the age of six.²⁹

Janssen (J&J) 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 (J&J) obtained the molecule patent in India¹⁴² and China.⁴³ This patent will block the development of generic formulations of ETV, unless licences – whether voluntary or compulsory – are issued. In India, the company has filed additional patent applications^{144,145} on new forms which, if granted, will extend its monopoly in India from 2021 to 2026. The basic patent on ETV has also been granted in both ARIPO and OAPI countries.⁴⁷

In August 2009, the company signed a royalty-free, non-exclusive agreement with Aspen covering all of sub-Saharan Africa for all ETV

formulations. Under this agreement, Aspen will handle regulatory and distribution activities only. The terms are not public and the geographical scope is limited – in 2011 Johnson & Johnson announced that least-developed countries were covered through this arrangement.¹⁰⁹ For details on this and other voluntary licences, see Annex 3.

In December 2011, J&J 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 J&J is ready to consider more open and transparent licencing mechanisms.



FOSAMPRENAVIR (FPV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2010 WHO Guidelines: Indicated for treatment for adults, adolescents and children.^{13,29}
- Originator company and product brand name: GlaxoSmithKline (GSK) and Vertex, Lexiva. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approved by the US Food and Drug Administration (FDA): October 2003.³⁰
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition for adults or the 3rd edition for children.^{31,32}
- World sales of originator product: Sales are not reported in the company's annual report.
- Patents: The basic patent was applied for by Vertex Pharmaceuticals in March 1998¹⁴⁶ and is due to expire in 2018. Fosamprenavir, a prodrug of amprenavir was developed and launched by GSK under licence from Vertex.¹⁴⁷ GSK also holds patents related to a crystalline form of the calcium salt of FPV,¹⁴⁸ due to expire in 2019.

PRICE INFORMATION

	Daily dose	ViiV
FPV 50mg/ml suspension (paediatrics)	12ml**	783 (0.179/ml)
FPV 700mg tablet	2*	1125 (1.541)

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

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

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 June 2012) 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.

SPOTLIGHT ON ACCESS ISSUES

Fosamprenavir (FPV) requires boosting with ritonavir (RTV), which increases the pill burden for patients, as there is no fixed-dose combination available for this product.

While regimens containing boosted FPV show good antiviral efficacy and are generally well tolerated in treatment-naïve patients, the experience of this drug in developed countries is limited and little comparative data are available in treatment-experienced patients.¹⁴⁹

FPV is not the preferred boosted protease inhibitor according to the 2010 WHO treatment guidelines for adults and adolescents, as it

is very expensive. There is no generic version of the drug.

Paediatrics

The 2010 WHO guidelines for infants and children state that FPV may be used in children above two years of age but requires co-administration with RTV.²⁹ A paediatric suspension of FPV is available, but its price is very high. In addition, there is no paediatric FDC available for this product with RTV, in either liquid or oral solid form.

In April 2012, the US FDA approved FPV for use in infants and children from four weeks of age and above.³⁰

Patents

Patent applications have been filed in many developing countries.

In China, South Africa, ARIPO and OAPI countries,¹⁵⁰ most patents have been granted. In June 2010, India granted a patent to Vertex Pharmaceuticals that covers fosamprenavir salts, including calcium, which is the marketed salt.¹⁵¹ Post-grant patent oppositions were filed by generic companies but their outcome is unknown at this time.¹⁵²

In Brazil, the basic patent was rejected by the patent office, although in December 2009 ViiV filed an appeal against the decision. Another patent application on calcium salt form was also rejected in Brazil.⁴⁷



INDINAVIR (IDV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2010 WHO Guidelines: Indicated for treatment for adults and adolescents.¹³
- Originator company and product brand name: Merck, Crixivan.
- First approved by US Food and Drug Administration (FDA): March 1996.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults.³¹
- World sales of originator product: Sales are not reported in the company's annual report.
- Patents: The basic patent was filed by Merck in 1992 and is likely to expire in November 2012.¹⁵³

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 June 2012) are in **bold**.

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

	Daily dose	Merck	Aurobindo	Hetero
IDV 400mg capsule	4*	394 (0.270)	268 (0.183)	430 (0.294)

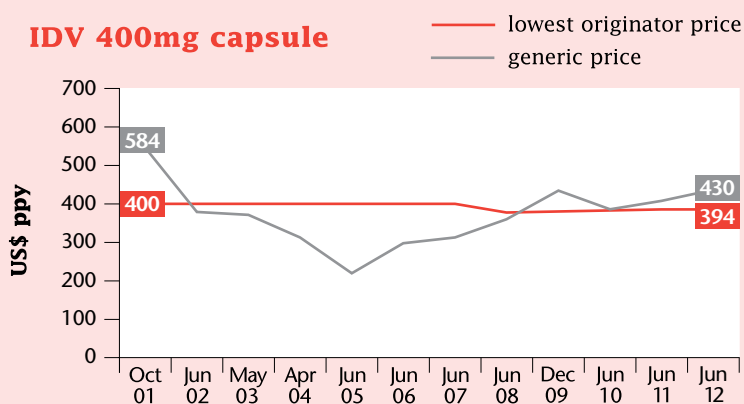
*The dose of IDV must be boosted with RTV 100mg twice a day.

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

As of June 2012, there are a couple of generic sources of IDV 400mg capsule which are quality-assured by US FDA or WHO prequalification, but only one of the manufacturers of the prequalified generics provided us with pricing information for this publication.

Since 2001, the originator price has decreased by 1.5%, while the generic price has dropped by 26%. However, the price of the generic is still higher than the originator.

IDV 400mg capsule



SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors, to be taken in combination with two NRTIs, neither of which is indinavir (IDV). They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). According to the 2010 WHO treatment guidelines for adults

and adolescents, IDV is not preferred because it is associated with a high risk of toxicity.¹³

Paediatrics

IDV is not available in easy-to-use paediatric formulations and lacks appropriate dosing information for children.²⁹

Patents

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

There are no patents in India, ARIPO and OAPI countries.



LAMIVUDINE (3TC)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO Guidelines: Indicated for first- and second-line treatment for adults, adolescents and children.^{13,29}
- 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 1995.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$110 million; 2010: \$186 million; 2009: \$197 million; 2008: \$225 million; 2007: \$309 million; 2006: \$398 million; 2005: \$398 million; 2004: \$549 million.^{33,36,37,38,154,155}
- Patents: As the molecular structure of emtricitabine (FTC) and 3TC are very closely related, the same patent covers both these drugs.^{156,157} The basic patent covering both FTC and 3TC was filed by IAF Biochem in 1990 and should therefore have expired in 2010 in countries with 20-year patent terms.¹⁵⁶

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 June 2012) are in **bold**.

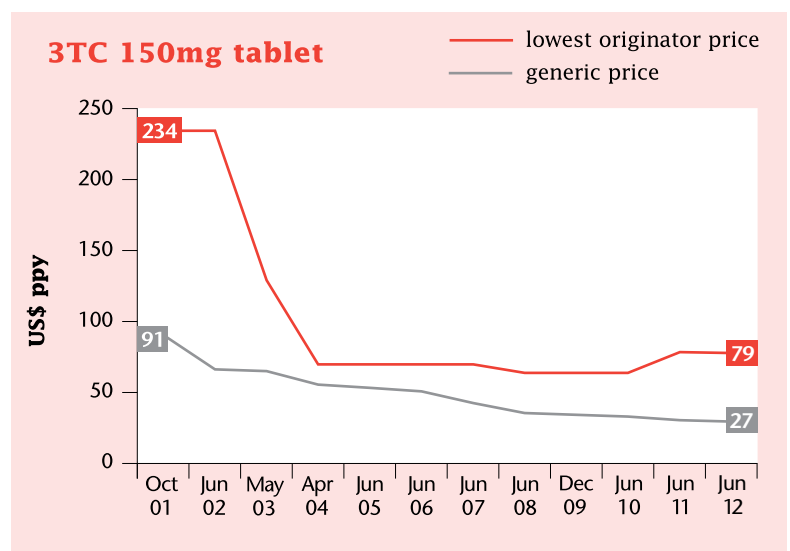
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Alkem	Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Ranbaxy	Strides
3TC 10mg/ml oral suspension (paediatrics)	10ml	212 (0.058/ml)		34 (0.009/ml)	30 (0.008/ml)	40 (0.011/ml)					
3TC 150mg tablet	2	79 (0.109)	43 (0.058)	29 (0.040)	32 (0.044)	34 (0.047)	32 (0.044)	30 (0.042)	27 (0.037)	28 (0.038)	28 (0.038)
3TC 300mg tablet	1				24 (0.067)	27 (0.075)			21 (0.058)		

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

As of June 2012, there are nine generic sources of 3TC 150mg tablet which are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2001, the originator price has decreased by 66% while the generic price has dropped by 70%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

Lamivudine (3TC) is a widely-used ARV both in first- and second-line regimens according to the WHO treatment guidelines for adults, adolescents and children.^{13,29} The drug is an important component of fixed-dose combinations (FDCs). Please refer to the drug profiles of the 3TC-based FDCs for further information on these combinations.

For the first-line treatment of adults and adolescents, the 2010 WHO treatment guidelines recommended 3TC or emtricitabine (FTC), together with tenofovir (TDF) or zidovudine (AZT) and efavirenz (EFV) or nevirapine (NVP).¹³

Importantly, according to the WHO treatment guidelines, FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.^{13,29}

According to the prices quoted by manufacturers, lamivudine-based FDCs are more affordable than emtricitabine-based FDCs.

Paediatrics

3TC is approved for use and is widely used in children. In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC to be given in an FDC with either abacavir (ABC), stavudine (d4T) or AZT and either an NNRTI or a PI in the first line.²⁹ 3TC can also be part of second-line regimens, depending on what has been used as first line.²⁹

There are two WHO-prequalified generic sources of the 3TC oral solution – the lowest reported price is US\$30 ppy.

WHO recommends FDCs be used whenever possible.²⁹ There are few paediatric double and triple FDCs containing 3TC.

Patents

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 is not under patent, such as India, Thailand and Brazil. A patent application on an oral formulation of 3TC was also filed in India.⁴⁷ In China, several patents were granted on 3TC, one of which expired in 2011.⁴³

GSK obtained a licence from IAF to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which are due to expire in June 2012.¹⁵⁸ GSK also applied for a new formulation patent in 1998. This patent was granted in Brazil, China and in ARIPO and OAPI countries.¹⁵⁹



LOPINAVIR/ RITONAVIR (LPV/r)

GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- 2010 WHO Guidelines: Indicated for second-line treatment for adults, adolescents and children.^{13,29} Indicated as first-line treatment for infants previously exposed to nevirapine (NVP).²⁹
- Originator company and product brand name: Abbott Laboratories, Kaletra/Aluvia.
- First approved by US Food and Drug Administration (FDA): September 2000 for soft-gel capsules; October 2005 for heat-stable tablets.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$1.170 billion; 2010: \$1.255 billion; 2009: \$1.366 billion; 2008: \$1.47 billion; 2007: \$1.32 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million.^{160, 161, 162, 163, 164}
- Patents: Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to lopinavir (LPV) was applied for by Abbott in 1996.¹⁶⁵ In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997¹⁶⁶ which are due to expire in 2017. An application for a patent on the LPV/r heat-stable tablet formulation was filed in 2004¹⁶⁷ which 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 June 2012) are in **bold**.

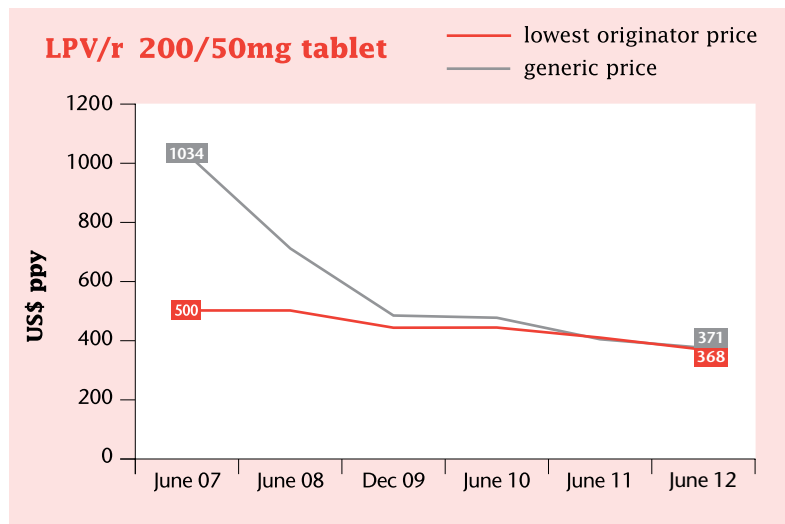
Please refer to Annex 2 for the conditions of eligibility set by individual companies, as well as for the incoterms associated with these prices.

	Daily dose	Abbott		Aurobindo	Cipla	Hetero	Matrix (Mylan)
		Category 1 countries	Category 2 countries				
LPV/r 80/20mg/ml oral solution (paediatrics)	4 ml	147 (0.101/ml)	296 (0.203/ml)				
LPV/r 100/25mg heat-stable tablet (paediatrics)	3	138 (0.126)	278 (0.254)	164 (0.150)			164 (0.150)
LPV/r 200/50mg heat-stable tablet	4	368 (0.252)	740 (0.507)	402 (0.275)	481 (0.329)	389 (0.267)	371 (0.254)

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

As of June 2012, there are four generic sources of LPV/r 200/50mg heat-stable tablet which are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

The price of the originator is lower than the generic although the margin has been reduced and the generic undercut the originator price once, in 2011. The originator price was US\$410 in 2011 and \$368 in 2012. The generic price dropped from \$402 in 2011 to \$371 in 2012. None of the manufacturers of the prequalified generics provided pricing information for LPV/r 133/33mg soft-gel capsules (that require cold chain) for this publication.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

Lopinavir/ritonavir (LPV/r) is one of two PIs recommended by WHO for second-line treatment, to be taken in combination with two NRTIs – the other being atazanavir (ATV) boosted with RTV.^{13, 29}

In November 2011, a first generic source of ATV/r was WHO-prequalified. The introduction of this heat-stable formulation represents a step forward for access to second-line ARVs, as it represents the first fixed-dose combination (FDC) alternative to heat-stable LPV/r, currently the most commonly used protease inhibitor. ATV/r has the added benefit of reducing the pill burden for patients – down from four pills a day for heat-stable LPV/r to one pill a day for ATV/r. 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 quoted for eligible countries by the originator, Abbott, remains marginally more affordable.

Paediatrics

Paediatric formulations exist, but are not adapted to the conditions of resource-limited settings. The LPV/r solution requires refrigeration until dispensing, after which it must be stored below 25°C for no more than six weeks. Furthermore, the solution consists of 42% alcohol and has an unpleasant taste.

There is therefore an urgent need for more adapted heat-stable paediatric formulations of LPV/r, such as soluble granules or sprinkles. Indeed, the WHO Paediatric Antiretroviral Working Group considers the development of a LPV/r 40/10mg heat-stable sprinkle to be a high priority.^{29, 229}

A heat-stable sprinkle in a paediatric dose of LPV/r 40/10mg (equivalent to 0.5ml liquid) is under development by a generic company.

Patents

In India, Abbott could not file a basic patent on LPV. However, the company has applied for several patents on the polymorphic forms of LPV¹⁶⁸ and RTV,^{169, 170, 171, 172} on the combination of LPV/r in a tablet formulation^{173, 174} and on the LPV process.

A number of these applications have been opposed by civil society organisations¹⁷⁵ and generic companies. Following a pre-grant opposition to the application related to the tablet formulation of LPV/r, the application was rejected by the Indian patent office.¹⁷⁶

While an appeal is pending to the rejection, Abbott has abandoned the two divisional patent applications it had filed on the tablet formulation of LPV/r.^{177, 178}

The Indian patent office also rejected a patent application on LPV crystalline polymorphs.¹⁷⁹

Abbott has also abandoned the applications related to RTV crystalline polymorph and their divisionals¹⁸¹ after further patent oppositions were filed by civil society organisations and generic companies.

Two of Abbott's applications related to a polymorph form of RTV¹⁸⁰ and a solid pharmaceutical dosage formulation are still however pending before the Indian patent office. In addition, key applications relating to the solid pharmaceutical dosage (tablet) formulation of LPV/r¹⁸² and to the LPV process¹⁸³ are also pending. If one of these patent applications is granted, current generic competition – which is

bringing prices substantially down as demand increases – will be under threat.

In Thailand, where Abbott holds patents, the Ministry of Public Health issued a compulsory licence in January 2007 – when the price of LPV/r stood at US\$2,200 ppy – to import more affordable generic versions of the drug from India.¹⁸⁴ Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies. Abbott's response was to withdraw all registration applications for its new products in Thailand, including the heat-stable LPV/r. Thailand today imports generic LPV/r from India for \$793 ppy.¹⁸⁵

In response to Thailand's compulsory licence, Abbott reduced the price for 40 middle-income countries for both the soft-gel and the heat-stable version to \$1,000 ppy, including Brazil which at the time was paying \$1,380. In 2005, the Brazilian government had entered into negotiations with Abbott to reduce the price of LPV/r and in June of the same year, the Ministry of Health declared the drug to be of public interest – 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 under the TRIPS agreement. In 2007, the National Federation of Pharmacists – on behalf of the Brazilian Network for

Continued above right ❖

⋮ *Continued from below left*

the Integration of Peoples – made a request to the Brazilian Prosecutor General to consider overturning the pipeline mechanism on the grounds that it is unconstitutional. A key argument in favour of overturning the mechanism is that these patents should not be granted in Brazil, since they were already in the public domain and that granting the patents in this way is against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court.¹⁸⁶ This case has not yet been heard.¹⁸⁷ However, in February 2012, the federal court of Rio de Janeiro¹⁸⁸ annulled the original patent granted in 1997 through the pipeline mechanism¹⁸⁹ following a nullity action filed by a generic manufacturer in September 2009.

The decision marks 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 longstanding 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 this 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 them have been opposed by civil society groups and generic companies. In November 2011, Brazilian civil society groups opposed¹⁹⁰ a patent covering the tablet heat-stable formulations

of both LPV/r and RTV.¹⁹¹ The move was an attempt to avoid monopoly extension over LPV/r and appropriation of ritonavir alone, 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 this opposition.¹⁹²

In November 2011, several public health groups launched a global campaign across twelve countries to challenge Abbott's patents on LPV/r via patent oppositions or requests for compulsory licences. The campaign is aimed at spurring competition through 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.¹⁹³



NEVIRAPINE (NVP)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 2010 WHO Guidelines: Indicated for first- and second-line treatment for adults, adolescents and children.^{13,29}
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune and Viramune XR.
- First approved by US Food and Drug Administration (FDA): June 1996.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2007: US\$412 million; 2006: \$370 million; 2005: \$386 million; 2004: \$378 million.^{194,195,196,197} After 2007, sales are not reported in the company's annual report.
- Patents: The basic patents on NVP were applied for by BI in November 1990 and expired in November 2010.¹⁹⁸ BI also was granted patents in 1998 on the hemihydrate form of NVP used in the suspension, which are due to expire 2018.¹⁹⁹ Additionally, BI applied for a patent on the extended release formulation of NVP in 2008, which is due to expire in 2028.²⁰⁰

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 June 2012) are in **bold**.

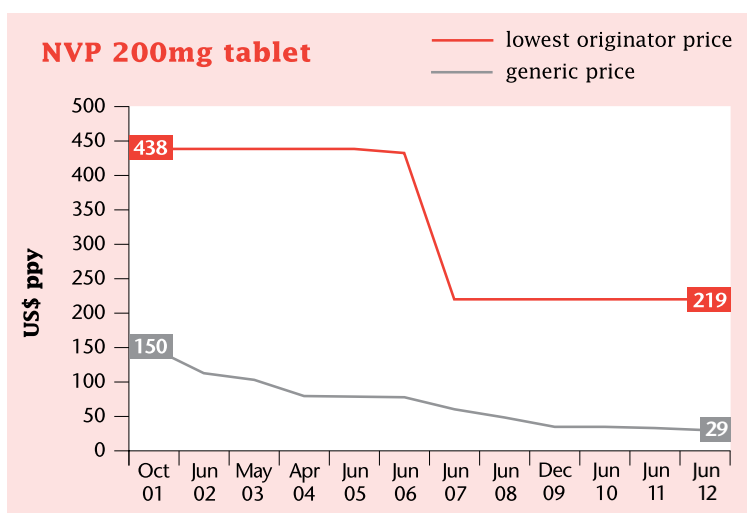
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Boehringer Ingelheim		Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Strides	Universal Corporation
		Category 1 countries	Category 2 countries										
NVP 10mg/ml suspension	20ml	380 (0.052/ml)	532 (0.073/ml)		64 (0.009/ml)	117 (0.016/ml)							
NVP 50 mg tablet for oral suspension (paediatrics)	4				66 (0.045)								
NVP 200 mg tablet	2	219 (0.300)	438 (0.600)	37 (0.051)	35 (0.048)	38 (0.052)	34 (0.047)	33 (0.046)	29 (0.040)	48 (0.066)	32 (0.044)	29 (0.040)	
NVP 200 mg capsule	2												30 (0.041)

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

As of June 2012, there are several generic sources of NVP 200mg tablet which 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 80%.



SPOTLIGHT ON ACCESS ISSUES

Nevirapine (NVP) is a widely-used ARV, predominately in first-line regimens. It has been an important component of the fixed-dose combinations (FDCs) that have fostered treatment scale-up in resource-limited settings. However, NVP interacts with one of the most commonly used TB drugs, rifampicin, requiring the patient to switch to efavirenz (EFV) during the course of TB treatment.

The price of NVP has dropped significantly due to generic competition, and is now available from several WHO-prequalified sources for less than US\$50 ppy.

WHO recommends fixed-dose combinations be used whenever possible – please refer to the relevant drug profiles for information on NVP-based combinations.

NVP single-drug formulations continue to have a role in PMTCT programmes in developing countries.²⁰¹

Paediatrics

NVP is approved for use and is widely used in children. In the 2010 WHO guidelines for infants and children, the recommendation for children from 12 months of age not exposed to NNRTIs is to be given NVP in addition to two NRTIs.²⁹

Currently, there are only two WHO-prequalified generic sources of the paediatric oral solution of NVP – price is an issue, and is much higher for formulations for children compared to those for adults.

The WHO Paediatric Antiretroviral Working Group considers the development of a NVP 20mg scored tablet to be a high priority.²⁹

Patents

Boehringer Ingelheim (BI) obtained the basic patent on NVP in several developing countries, but no patent could be obtained in countries such as India, Brazil, China or Thailand, which were not granting patents on medicines before the full implementation of the TRIPS agreement. Many developing countries, where NVP is under patent, import generic versions by making use of TRIPS flexibilities. The basic patent expired in many countries in 2010, including in ARIPO countries in November 2010.⁴⁷ A similar patent was also granted in OAPI countries.

In African countries, low-income countries and least-developed countries, BI has a non-assert policy for its patents, which overcomes some of the barriers to

generic competition, but only for the countries concerned. Many developing countries in Asia, Latin America and the Caribbean are excluded from the policy. 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,²⁰² which relates to the paediatric suspension. Civil society groups filed a pre-grant opposition to BI's application in May 2006.²⁰³ In June 2008, the application was rejected by the Indian patent office,²⁰⁴ 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 an HIV medicine to have been rejected as a result of a pre-grant opposition process, in accordance with the 2005 Indian Patents Act.²⁰⁵

In 2008, BI filed a Patent Cooperation Treaty (PCT)²⁰⁶ application for an extended release formulation of NVP – in India the same application was published in 2010.²⁰⁷ This application relates to the once-a-day dosing of NVP.



RALTEGRAVIR (RAL)

GENERAL INFORMATION

- Therapeutic class: Integrase inhibitor.
- 2010 WHO Guidelines: Listed in the WHO guidelines for adults and adolescents as a potential third-line treatment when taken with boosted darunavir (DRV) and etravirine (ETV).¹³
- 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 17th edition for adults or the 3rd edition for children.^{31,32}
- World sales of originator product: 2011: US\$1.4 billion; 2010: \$1.1 billion; 2009: \$752 million; 2008: \$361 million; 2007: \$41 million.^{208,209,210,211}
- Patents: The basic patent was applied for in October 2002 by the Institute for Research in Molecular Biology, one of Merck's research sites.²¹² 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 2025.²¹³

PRICE INFORMATION

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

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 June 2012) 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
RAL 400mg tablet	2	675 (0.925)

SPOTLIGHT ON ACCESS ISSUES

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

The price of the innovator product has not changed since last year. Currently, there is no generic version of RAL.

Paediatrics

According to 2010 WHO treatment guidelines for infants and children, RAL and darunavir (DRV) may be used for older children as a third-line regimen.²⁹

In December 2011, the US FDA approved dosing recommendations for RAL for paediatric patients aged two to 18 years and weighing at least 10kg. In addition, a 100mg scored chewable tablet and 25mg chewable tablet were approved for use in paediatric patients.³⁰

Patents

Merck and IRBM applied for international patent applications^{214,215,216} under the Patent Cooperation

Treaty (PCT) that facilitated the filing of these patent applications in many PCT member states, including some developing countries with generic drug manufacturing capacity like Brazil, China, India and South Africa.

In India, IRBM was granted a patent in December 2007 which will not expire until 2022.²¹⁷ In India, an application on the potassium salt of RAL²¹⁸ is also pending for review before the Indian patent office and warrants a pre-grant opposition. If granted, Merck's monopoly in India will be extended by an additional five years to 2027. In India, Merck is currently charging \$1800 ppy.²²²

In Brazil, the Ministry of Health has announced that it is working on a technology transfer agreement with Merck for RAL.²¹⁹ The terms of this agreement are not public. In 2010, the Brazilian government was paying US\$5,870 ppy, a price that is expected to decrease to \$4,000 with the technology transfer in 2015.²²⁰ See Annex 3 for details.

This approach – which is unlikely to ensure that prices are reduced to a level that is possible through unrestricted generic competition – may well establish a precedent for

accessing other newer medicines in the future, both in Brazil and beyond. As Brazil has one of the oldest HIV patient cohorts in developing countries, the need to access newer HIV medications is occurring earlier than in many other countries. The access challenges Brazil experiences today will be faced by other developing countries in coming years and Brazil's actions to improve the accessibility and affordability of RAL and other newer 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 medicine²²¹ 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).
- 2010 WHO Guidelines: Indicated for second-line treatment as a booster for adults, adolescents and children.^{13,29}
- Originator company and product brand name: Abbott Laboratories, Norvir.
- First approved by US Food and Drug Administration (FDA): March 1996 for the oral solution; June 1999 for capsules.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: 2004: US\$194 million; 2003: \$93 million; and 2002: \$122 million.²²³ After 2004, sales are not reported in the company's annual report.
- Patents: The basic patent was applied for by Abbott in 1993 and is due to expire in 2013–14.²²⁴ Subsequently, Abbott applied for patents related to polymorphic forms of RTV^{225,226} and to a soft-gel capsule formulation.²²⁷ 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 June 2012) are in **bold**.

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

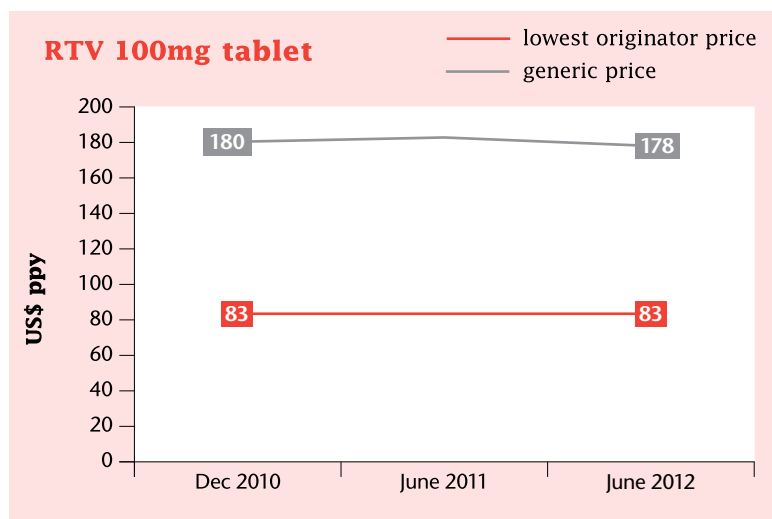
	Daily dose	Abbott		Matrix (Mylan)
		Category 1 countries	Category 2 countries	
RTV 80mg/ml oral solution (paediatrics)	xx	(0.091/ml)	Case-by-case basis	
RTV 100mg heat-stable tablet	2*	83 (0.114)	Case-by-case basis	178 (0.243)

* 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 June 2012, there is only one generic source of RTV 100mg heat-stable tablet which is quality-assured by WHO prequalification.

Since 2010, the generic price has decreased by 1%. The originator price is 53% lower than the generic price.



SPOTLIGHT ON ACCESS ISSUES

Ritonavir (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 of the most commonly used FDC that contains RTV, the heat-stable combination with lopinavir (LPV/r), there is only one generic manufacturer of the stand-alone RTV 100mg tablet. More competition is needed to help decrease the price.

Stand-alone heat-stable RTV is particularly needed for additional boosting for patients also taking TB treatment, and for boosting darunavir (DRV) as a part of a third-line regimen.

Paediatrics

RTV is approved for use in children from one month of age by the US FDA.²²⁸

A liquid formulation is available. However, the solution has a bitter aftertaste and contains 43% alcohol, and hence is not adapted for children. No generic liquid formulation has yet been

prequalified. There is an urgent need for a heat-stable 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.²²⁹

Patents

Patent filing on RTV has increased dramatically since 1993 and it now includes more than 800 patent families.²³⁰

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 and divisional applications on new forms of RTV that are pending before the Indian patent office.^{231,232,233,234} Several pre-grant oppositions to the RTV polymorph were filed by civil society organisations and generic companies and have been rejected by the patent office²³⁵ and thereafter abandoned by Abbott.²³⁶ This opposition has safeguarded the supply from Indian generic producers, for patients both in India and throughout the developing world.

Patents related to polymorphic forms of RTV have also been filed in other middle-income countries. In Brazil, the patent application on crystalline polymorph was rejected.⁴⁷ RTV is locally produced, as the basic patent is being opposed by Brazilian generic manufacturers in the courts. In China, a patent on crystalline polymorph was granted in China.⁴⁷

In April 2010, Ecuador issued its first compulsory licence. It allowed Eskegroup SA – the local distributor for Cipla – to manufacture, offer for sale, sell, use or import RTV or compositions including RTV, for public non-commercial use, against the payment of royalties to Abbott until the patent expiration date in 2014.²³⁷ The compulsory licence, which followed a decree by the President in October 2009 declaring access to essential medicines to be in the public interest allowed the national intellectual property office to issue compulsory licences, based on Article 31 of the TRIPS agreement.²³⁸ According to the Ministry of Health, the compulsory licence already has yielded savings of US\$150,000.



SAQUINAVIR (SQV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- 2010 WHO Guidelines: Indicated for treatment in HIV/TB co-infected adults and adolescents, together with two NRTIs if rifabutin is not available.¹³ Not recommended for children under 16 years of age and/or weighing less than 25kg.²⁹
- Originator company and product brand name: Roche, Invirase.
- First approved by US Food and Drug Administration (FDA): December 1995.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: Sales are not reported in the company's annual report.
- Patents: The basic patent was applied for by Roche in 1990²³⁹ and should have expired in 2010 in countries not granting patent extensions. A patent related to oral dosage form was filed by Roche in 2004 and is due to expire in 2024.²⁴⁰ Another patent on an improved composition was filed which will not expire before 2016.⁴⁷

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 June 2012) 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	Roche	
		Category 1 countries	Category 2 countries
SQV 200mg hard capsule	10*	1489 (0.408)	2981 (0.817)
SQV 500mg tablet	4*	1366 (0.935)	2978 (2.040)

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

SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). While the 2010 guidelines still indicate saquinavir (SQV) boosted with ritonavir as an alternative to other PIs, it is not a preferred option as the pill burden is high.¹³

There are no generic formulations of this product.

Paediatrics

SQV has not been approved for use in children by the US FDA or EMA but is approved for those over 16 years

of age and/or weighing 25kg. It is not a preferred option in the WHO paediatric treatment guidelines as it is not available in easy-to-use paediatric formulations and lacks appropriate dosing information for children.²⁹

Patents

The basic patent was rejected in Brazil where this medicine is locally produced. It was however granted in many other countries including China, South Africa and OAPI countries. These patents should have expired by now.

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

In India, three patents^{241,242,243} on improved compositions and SQV mesylate have been granted, expiring in 2024. However, generic versions of SQV are available in India for the Indian market as a result of the automatic licencing section of the Indian patent law. This allows Indian companies which had invested in or had started producing the generic version of a patented drug before 1 January 2005 to continue to produce the generic version of the patented medicine.

The patent on the improved composition form has also been granted in OAPI countries.⁴⁷



STAVUDINE (d4T)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO Guidelines: Indicated for first-line treatment for children as part of a nucleoside backbone regimen.²⁹ It is indicated for treatment for adults but is not preferred over zidovudine (AZT) or tenofovir (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC) as a first-line treatment regimen with an NNRTI.
- WHO recommends a move away from d4T use in first-line treatment.¹³
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- First approved by US Food and Drug Administration (FDA): December 1994.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32}
- World sales of originator product: Sales are not reported in the company's annual report.
- Patents: Yale University applied for a patent on the antiretroviral activity of d4T in December 1987, mostly in developed countries.²⁴⁴ Patent protection was extended until the end of 2008 in the US and until 2011 in most European countries. Patents should have expired in most other countries at this point.

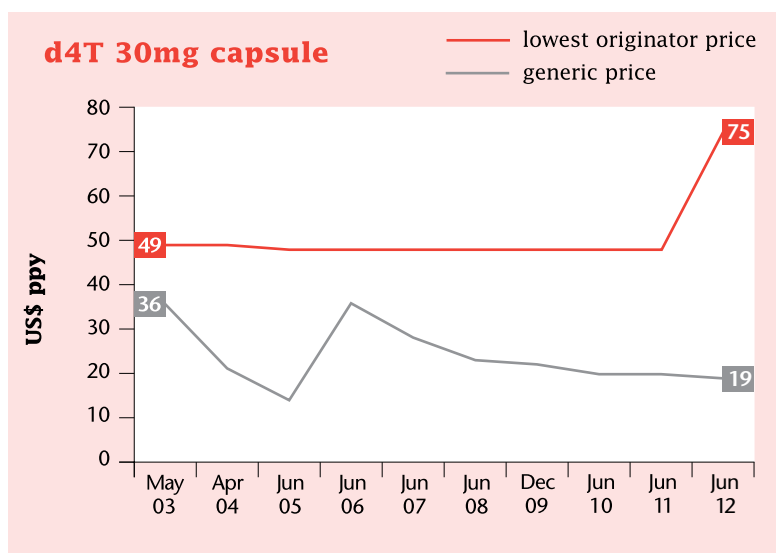
PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of June 2012) are in **bold**.

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

	Daily dose	Bristol-Myers Squibb		Aspen	Aurobindo	Cipla	Ranbaxy	Strides
		Category 1 countries	Category 2 countries					
d4T 1mg/ml powder for oral solution (paediatrics)	20ml	55 (0.008/ml)	Case-by-case basis		55 (0.008/ml)	68 (0.009/ml)		
d4T 15mg capsule (paediatrics)	xx			(0.027)	(0.025)			
d4T 20mg capsule (paediatrics)	xx		(0.103)	(0.031)	(0.027)			
d4T 30mg capsule	2		75 (0.103)		21 (0.028)		30 (0.042)	19 (0.027)
d4T 40mg capsule	2		75 (0.103)					



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

As of June 2012, there are several generic sources of d4T 30mg capsule which are quality-assured by US FDA and WHO prequalification, but not all of the manufacturers of the prequalified generics provided pricing information for this publication. The lowest price is shown here.

Since 2003, the generic price has decreased by 47% whereas the originator price has increased by 35%. Note however that the price provided by Bristol-Myers Squibb is only available for certain countries (see Annex 2).

Continued overleaf ❖❖❖

SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

As the considerable number of generic manufacturers of d4T shows, the drug is still widely available however and used in many settings as a first-line option, in combination with 3TC and EFV. Please refer to the d4T-based FDC drug profiles for additional information.

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF,^{13,245} due to funding constraints, a number of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens.

Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends d4T as one of the possible NRTIs to be given with 3TC and either an NNRTI or a PI in the first line.²⁹

There are several generic paediatric formulations available on the market, including two WHO-prequalified 3TC/d4T combinations. Please refer to the relevant drug profiles for additional information.

Patents

The result of US public sector research, d4T was originally synthesised by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.²⁴⁶ Bristol-Myers Squibb (BMS) produces d4T under a marketing and distribution licence from Yale University.

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

In South Africa, where BMS marketed d4T under an exclusive licence from Yale, the drug was 34 times more expensive than generic versions available in other countries. This prompted controversy in March 2001, particularly as the medicine had been developed with public funds. After pressure from researchers, students, and access advocates, Yale renegotiated its licence with BMS to allow the importation of more affordable generic versions of d4T to South Africa.²⁴⁶



TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION

- Therapeutic class: Nucleotide reverse transcriptase inhibitor (NtRTI).
- 2010 WHO guidelines: Indicated for first- and second-line treatment for adults and adolescents.¹³
- Originator company and product brand name: Gilead, Viread.
- First approved by US Food and Drug Administration (FDA): October 2001.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults.³¹
- World sales of originator product: 2011: US\$738 million; 2010: \$732 million; 2009: \$667 million; 2008: \$621 million; 2007: \$613 million; 2006: \$689 million; 2005: \$778 million; 2004: \$783 million.^{128, 129, 130, 131, 132, 133, 247, 248}
- Patents: The basic patent on tenofovir was applied for by the Academy of Sciences of the former Czechoslovakia in 1986. It has now expired in most countries.²⁴⁹ Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997²⁵⁰ and to the fumarate salt of tenofovir disoproxil in 1998.²⁵¹ 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 2024.⁴⁷

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 June 2012) are in **bold**.

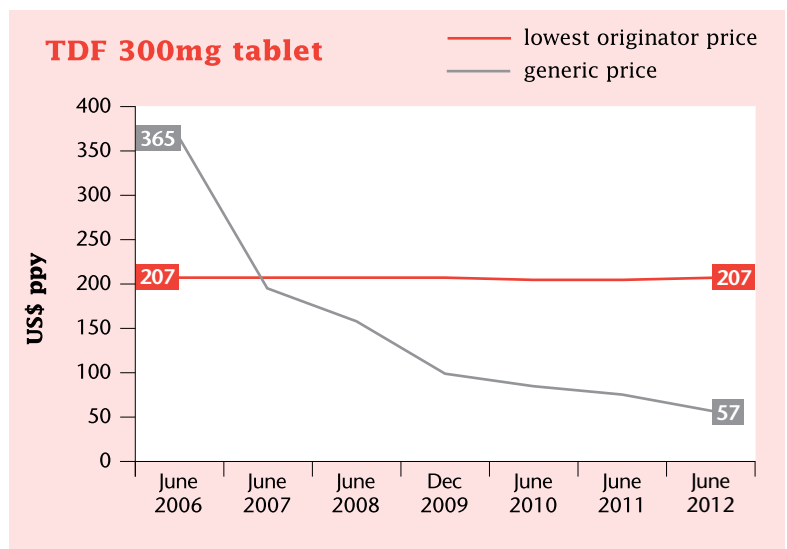
Please refer to Annex 2 for the conditions of eligibility set by individual companies, as well as for the incoterms associated with these prices.

	Daily dose	Gilead		Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy	Strides
		Category 1 countries	Category 2 countries							
TDF 300mg tablet	1	207 (0.567)	365 (1.000)	87 (0.237)	73 (0.200)	67 (0.183)	59 (0.162)	64 (0.175)	60 (0.165)	57 (0.157)

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

As of June 2012, there are six generic sources of TDF 300mg tablet which are quality-assured by US FDA and WHO prequalification.

Since 2006, the generic price has decreased by 84%. The originator price has remained constant for low-income countries (see Annex 2 for a list of these countries).



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SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

TDF is also recommended as the NRTI backbone in second-line treatment if d4T or AZT have been used in the first line, and is combined with either 3TC or FTC, to which a boosted protease inhibitor should be added.¹³

Based on WHO guidelines, TDF is preferred over AZT if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.¹³

TDF is also active against the hepatitis B virus (HBV) and therefore plays an important role in co-infected patients. The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.¹³

There are several prequalified generic versions of TDF and the lowest provided price is US\$57 ppy. Please refer to the drug profiles of TDF-based FDCs for more information.

Paediatrics

In January 2012, the US FDA approved Gilead's TDF for use in patients above the age of two. Approved formulations are a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.²⁵²

The approval of TDF use in children is a step forward as it opens up the possibility of aligning first-line ART for adults and children over three.

This would simplify treatment options for all and potentially simplify drug procurement for HIV programmes.

Patents

Thanks to generic production that started in India in 2005 and to the patent oppositions filed by civil society groups in 2006²⁵⁵ and 2007²⁵⁶ to safeguard production, the price of TDF fell dramatically between 2005 and 2010. In a major victory for access to medicines, in September 2009 the Indian patent office rejected several patent applications relating to the prodrug,²⁵⁷ the fumarate form,²⁵⁸ the intermediate,²⁵⁹ and to the combination of TDF with FTC and the once-a-day pill TDF/FTC/EFV.²⁶⁰ The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law.^{257, 258, 259}

Nevertheless, divisional applications have already been filed by Gilead for key applications covering the prodrug²⁶¹ and the fumarate salt,²⁶² as well as the combinations of TDF with FTC, EFV and lopinavir/ritonavir (LPV/r).^{263, 264} The divisional application on the prodrug form has been rejected. The divisional applications on the key application covering the fumarate salt have all been opposed by generic companies.

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.²⁷⁰ In April 2008, the government declared TDF as a medicine of public interest for priority examination purposes, and in September 2008, the Brazilian patent office published the patent rejection. However, in January 2010, Gilead launched a legal challenge

against the patent office's decision. Gilead also requested a divisional patent, which was opposed by civil society groups²⁷¹ and in another victory for access to medicines, was rejected in May 2011.²⁷²

While the patent oppositions by Indian and Brazilian civil society to Gilead's patent applications were still pending – and Gilead's monopoly in those countries therefore unsecured – the company signed voluntary licencing (VL) agreements in 2006 with key generic manufacturers in India and one in South Africa. One generic manufacturer, Cipla, did not accept the VL and instead opted to file patent oppositions to protect the manufacture and availability of its generic TDF, both domestically and for export.

Under the terms of the 2006 VL, Gilead retained the control over the manufacture and distribution of the active pharmaceutical ingredient and the finished product. Importantly, a number of countries, including middle-income countries with substantial HIV burdens, were excluded.²⁶⁵ 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.¹⁴⁰

In July 2011, Gilead signed a further licence agreement with the Medicines Patent Pool authorising the Pool to sub-licence 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

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⋮ *Continued from below left*

products in a once-daily, single tablet regimen, known as the ‘Quad’ (TDF/FTC/COBI/EVG) – to generic manufacturers.

Uniquely, the full terms of the licence have been made publically available.²⁶⁶ The licences are non-exclusive, non-transferable and non-sub-licencable. For TDF and combinations that include TDF, the royalty rate is 3%, which will increase to 5% if a patent is granted 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 – except for paediatric products. For TDF, the list of eligible territories has been increased from the 95 territories covered by Gilead’s 2006 licences, to 112 territories. Licensed manufacturers are still unable however 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. 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 and combination patents are also filed in India and Indonesia. The fact that TDF is not widely patented reveals to what extent Gilead is seeking to control the market even in the absence of a patent. The licence with the Pool also retains the restrictions in the 2006 licence on the manufacture and supply of APIs.

Countries that are excluded from the licences, and which have no patents on TDF, can either choose to

locally produce – provided they have sufficient manufacturing capacity and can identify and access an alternative source of API – or to source TDF from the two Indian generics that are not Gilead sub-licences. Countries that are excluded from the licences but that have or will have patents on TDF will have to rely on use of compulsory licences. In that respect the Pool licence is interesting, in that it explicitly allows a licensee to supply an excluded country if a compulsory licence has been granted, 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.²⁶⁷ This feature of the Gilead-Patent Pool licence, known as ‘unbundling’, allows generic companies to terminate the TDF component of the 2006 licence and retain the licence for the remaining products. Aurobindo and MedChem therefore terminated their previous TDF licence with Gilead, whilst licencing 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 on the very same products in July 2011, but outside of the Pool. Indeed, on the same day the Gilead Medicines Patent Pool licences were made public, Gilead also announced it had signed separate (in other words, bilaterally, and not via the Pool) licencing agreements with four ‘preferred’ Indian generic manufacturers.²⁶⁸ The licences cover TDF, FTC and 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 from conversations with 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, the licensee cannot make use of it).

For details of voluntary licences see Annex 3.

Brazil, one of the excluded countries from both the 2006 and the 2011 licences, is today paying \$715 ppy for TDF,²⁶⁹ following negotiations with Gilead. This price is substantially higher than the lowest WHO-prequalified generic price available. In February 2011, the Government announced the beginning of local production of TDF through a partnership between Gilead and Brazilian public and private manufacturers.²⁷³

This deal is particularly significant – 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 TDF²⁷⁴ 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 64,000 people taking TDF,²⁷⁴ 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/rilpivirine (RIL) which will not expire before 2024 and 2026 respectively in countries where granted.^{253,254}



ZIDOVUDINE (AZT or ZDV)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- 2010 WHO Guidelines: Indicated for first- and second-line treatment for adults, adolescents and children.^{13,29}
- 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 1987.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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: 2005: US\$84 million; 2004: \$80 million. After 2005, sales are not reported in the company's annual report.^{35,36}
- Patents: Glaxo Wellcome filed patents on AZT for the treatment of HIV in 1985.²⁷⁵ 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 June 2012) are in **bold**.

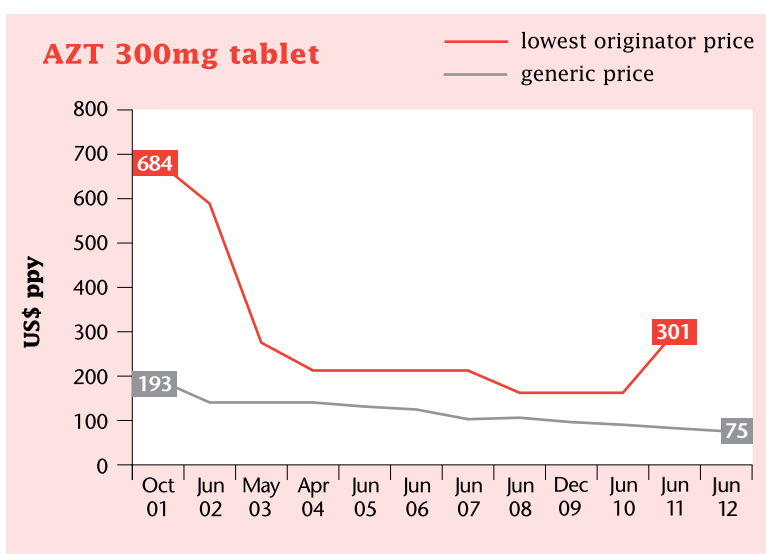
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Ranbaxy
AZT 10mg/ml oral solution (paediatrics)	24 ml	377 (0.043/ml)	107 (0.012/ml)	82 (0.009/ml)	106 (0.012/ml)				
AZT 60mg tablet (paediatrics)	4								73 (0.050)
AZT 100mg capsule (paediatrics)	xx	(0.184)		(0.048)	(0.055)				
AZT 100mg tablet (paediatrics)	xx								(0.065)
AZT 250mg capsule (paediatrics)	xx	(0.299)							
AZT 300mg tablet	2		100 (0.136)	85 (0.117)	85 (0.117)	83 (0.114)	82 (0.112)	82 (0.112)	75 (0.103)

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

As of June 2012, seven generic sources of AZT 300mg tablet are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

The originator company has discontinued production of the 300mg tablet this year and as displayed in the graph, the data for the price stops in 2011. Since 2001, the generic price has decreased by 61%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³ AZT is also recommended for second-line treatment if TDF has been used in first-line regimen.¹³

Based on WHO guidelines, TDF is preferred over AZT if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.¹³

This year, ViiV decided to cease production of the 300mg tablet. Production of the other strengths

(100mg and 250mg capsules) as well as AZT-based fixed-dose combinations will continue. There are several WHO-prequalified generic sources of this drug.

AZT single-drug formulations continue to have a role in PMTCT programmes in developing countries.²⁰¹

Paediatrics

AZT is approved for use and is widely used in children.²⁷⁷

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT as the preferred NRTI to be given with 3TC and either an NNRTI or a PI in the first line. AZT can also be part of second-line regimens, depending on what has been used as a first line.²⁹

Toxicity risks are associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.²⁹

There are already two WHO-prequalified generic sources of the AZT 10mg/ml oral solution and 100mg capsule.

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 AIDS and brought the drug onto the market in 1987 as one of the most expensive ever sold.

Patents have expired in most countries at this point.



ABACAVIR/ LAMIVUDINE (ABC/3TC)

GENERAL INFORMATION

- Therapeutic class: Two NRTIs in a double fixed-dose combination.
- 2010 WHO guidelines: ABC/3TC can be used with nevirapine (NVP) or efavirenz (EFV) or lopinavir/ritonavir (LPV/r) as a first-line treatment option. It is also indicated as part of a triple nucleoside regimen together with zidovudine (AZT) for individuals who are unable to tolerate or have contra-indications to triple NRTI-based regimens.¹³ ABC/3TC is the preferred NRTI backbone option for second-line ART for infants and children after failure on a first-line AZT- or stavudine (d4T)-based regimen.²⁹
- Originator company and product brand name: GlaxoSmithKline (GSK), Kivexa (EU), 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 2004.³⁰
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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: 2011: US\$994 million; 2010: \$899 million; 2009: \$834 million; 2008: \$721 million; 2007: \$641 million; 2006: \$475 million; 2005: \$233 million.^{33,35,36,37,38,155}
- Patents: Most patents on ABC or 3TC also affect this combination. In addition,²⁷⁸ GSK applied for patents more specifically related to the combination. The patent expiry dates related to this combination are 2016 in the US and 2019 in the EU.³⁸

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 June 2012) are in **bold**.

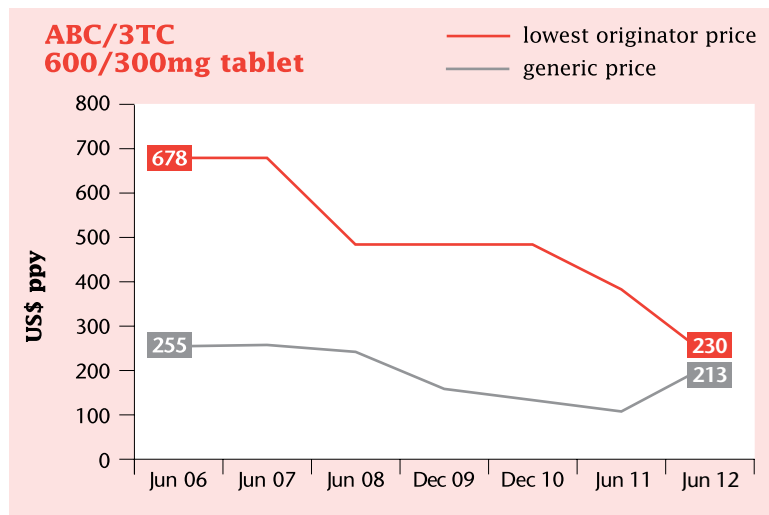
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Aurobindo	Cipla	Matrix (Mylan)
ABC/3TC 60/30mg tablet (paediatrics)	4		164 (0.113)	175 (0.120)	140 (0.096)
ABC/3TC 600/300mg tablet	1	230 (0.629)	213 (0.583)	389 (1.067)	268 (0.733)

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

As of June 2012, there are three generic sources of ABC/3TC 600/300mg tablets which are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2011, the generic price has increased by 47%. 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.



SPOTLIGHT ON ACCESS ISSUES

Price remains an issue with the abacavir/lamivudine (ABC/3TC) 600/300mg FDC. The current lowest generic price ppy is still more than double the lowest prequalified generic price ppy for the zidovudine/lamivudine (AZT/3TC) 300/150mg FDC tablet.

Generic companies are quoting much higher prices in comparison to last year – up from US\$112 ppy in 2011, to \$213 in 2012 (a 47% increase).

Paediatrics

ABC/3TC is a preferred first-line regimen for HIV/TB co-infected young children.²⁹

Despite ABC/3TC being an important treatment option in infants and children,²⁹ price remains an issue, as the lowest prequalified generic price ppy is still more than double the lowest prequalified generic price ppy for the AZT/3TC 60/30mg tablet.

The Paediatric Antiretroviral Working Group of WHO considers the development of a scored adult FDC of ABC/3TC 300/150mg tablet, for use in children weighing over 25kg, to be a high priority.²⁹

Patents

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. See the individual drug profiles for further details.



LAMIVUDINE/ STAVUDINE (3TC/d4T)

GENERAL INFORMATION

- Therapeutic class: Double fixed-dose combination of two NRTIs.
- 2010 WHO guidelines: Indicated for infants and infants and children starting treatment, although the preferred first-line NRTI is lamivudine/zidovudine (3TC/AZT), with 3TC/d4T only being the second choice, along with lamivudine/abacavir (3TC/ABC).²⁹ This combination is also indicated for first-line treatment for adults, but the preferred regimen is TDF- or AZT-based.¹³ WHO recommends a move away from d4T use in first-line regimens.¹³
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.
- Patents: Individual patents on 3TC or d4T also affect this combination.
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.

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 June 2012) 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.

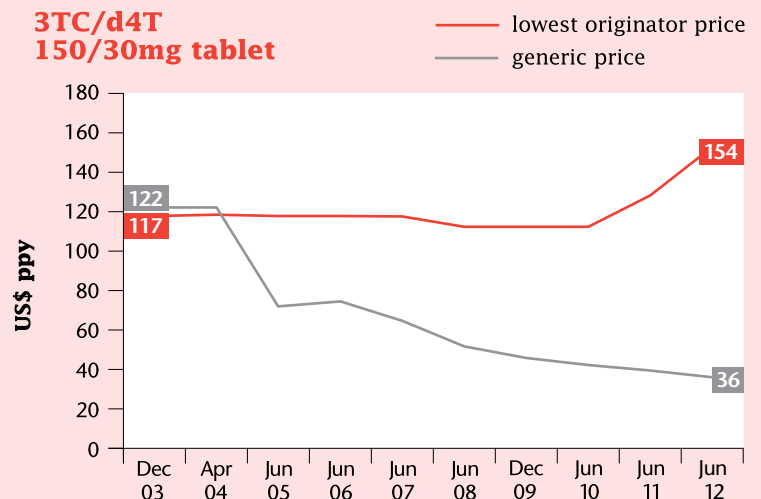
	Daily dose	Cipla	Hetero	Matrix (Mylan)	Ranbaxy	Strides
3TC/d4T 30/6mg dispersible tablet (paediatrics)	4	46 (0.032)				
3TC/d4T 60/12mg dispersible tablet (paediatrics)	2	40 (0.055)				
3TC/d4T 150/30mg tablet	2	40 (0.055)	39 (0.053)	37 (0.050)	39 (0.053)	36 (0.049)

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

As of June 2012, there are five generic sources of 3TC/d4T 150/30mg tablet which 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 2003, the originator price has increased by 24% (between 2011 and 2012 alone it increased by 17%) whereas the generic price has dropped by 70%.

3TC/d4T 150/30mg tablet



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT)- or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF,^{13,245} because of funding concerns, a number

of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens.

Paediatrics

3TC/d4T is recommended in the WHO 2010 guidelines for antiretroviral therapy for HIV in infants and children, as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.²⁹

There is currently only one WHO-prequalified generic manufacturer

of the paediatric formulations, for both the 30/6mg and for the 60/12mg tablets.

Patents

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

This FDC is not available in countries, however, where one or both medicines are under patent. Please refer to individual drug profiles for further information.

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

GENERAL INFORMATION

- Therapeutic class: Two NRTIs and one NNRTI in a triple fixed-dose combination.
- 2010 WHO guidelines: Indicated for first-line treatment for children.²⁹ This regimen is indicated in adults, but not preferred over first-line tenofovir (TDF) and zidovudine (AZT)-based regimens.¹³ WHO recommends a move away from d4T use in first-line regimens.
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.^{31,32}
- Patents: Individual patents on 3TC, d4T or NVP also affect this combination. Cipla first developed the fixed-dose combination and applied for patents in several African countries.²⁷⁹

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 June 2012) 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.

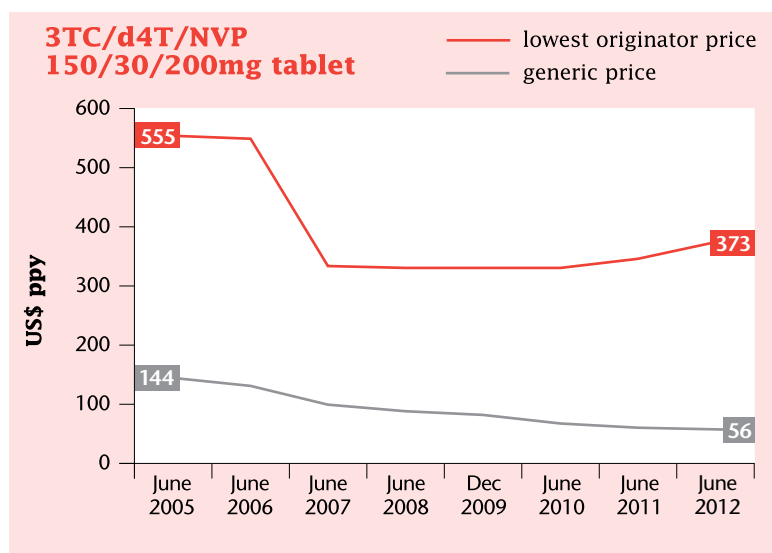
	Daily dose	Cipla	Hetero	Ranbaxy	Strides	Varichem
3TC/d4T/NVP 30/6/50mg dispersible tablet (paediatrics)	4	56 (0.038)				
3TC/d4T/NVP 60/12/100mg dispersible tablet (paediatrics)	2	52 (0.072)				
3TC/d4T/NVP 150/30/200mg tablet	2	61 (0.083)	61 (0.083)	62 (0.085)	56 (0.077)	61 (0.083)

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

As of June 2012, there are five generic sources of 3TC/d4T/NVP 150/30/200mg tablet which 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.

Since 2005, the originator price has decreased by 32% whereas the generic price has dropped by 61%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF,^{13,245} because of funding concerns, a number of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens.

Paediatrics

Despite this combination being recommended in the WHO 2010 guidelines for first-line antiretroviral therapy for HIV in children above the age of 12 months, there is only one WHO-prequalified generic manufacturer of either the 30/6/50mg and the 60/12/100mg tablets.²⁹

According to WHO, these FDCs are key for children co-infected with TB below three years of age.²⁹

Patents

Cipla was first able to develop this combination because none

of the individual components were patented in India. Many other 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 thus 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.



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

GENERAL INFORMATION

- Therapeutic class: Two NRTIs (in a double fixed-dose combination) with one NNRTI in a co-pack.
- 2010 WHO guidelines: 3TC/d4T is indicated as the nucleoside backbone regimen for infants and infants and children starting treatment, although the preferred first-line NRTI is lamivudine/zidovudine (3TC/AZT), with 3TC/d4T only being the second choice, along with lamivudine/abacavir (3TC/ABC).²⁹ This regimen is indicated for treatment for adults but is not preferred over the first-line treatment regimen combining AZT or tenofovir (TDF) with 3TC or emtricitabine (FTC) and an NNRTI.¹³ WHO recommends a move away from d4T use in first-line regimens.
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations.^{31,32}
- Patents: Individual patents on 3TC, d4T or EFV also affect this combination.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of June 2012) 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.

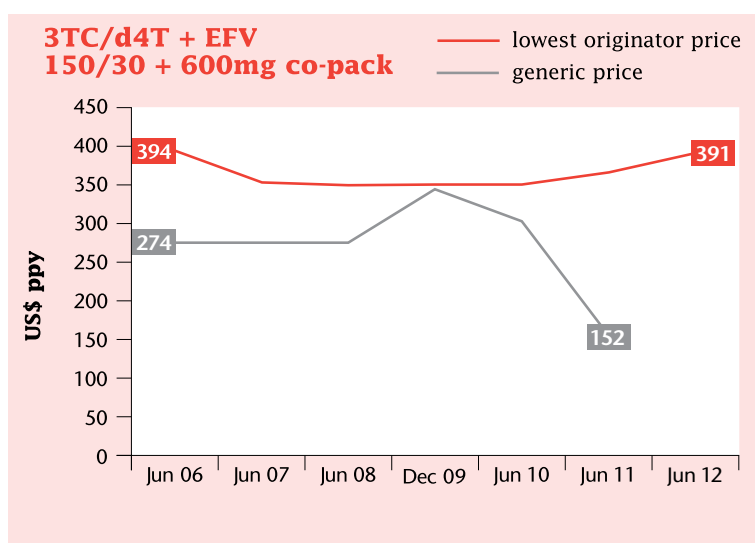
	Daily dose	Strides
3TC/d4T + EFV 150/30 + 600mg tablets (co-pack)	1 kit (2 tablets)	213 (0.583)

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

As of June 2012, there is only one generic source of 3TC/d4T + EFV 150/30 + 600mg co-pack, which is quality-assured by WHO prequalification but the manufacturer of the prequalified generic did not provide us with pricing information for this publication. The graph only charts the price of the generic product until 2011 as no pricing information was provided this year for the prequalified source.

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

Since 2006, the combined price of the originator products has decreased by only 0.76%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

Despite the better efficacy, reduced side effects and reduced pill burden associated with TDF,^{13,245} because of funding concerns, a number

of countries are at risk of slowing down the move from d4T-based regimens to TDF- or AZT-based regimens.

For this year's publication, no pricing information was provided for the WHO-prequalified generic source, and therefore no pricing analysis is possible.

Paediatrics

Despite this combination being recommended in the WHO 2010 guidelines for first-line antiretroviral therapy for HIV in children of three

years of age and above, and in those co-infected with TB, there is currently no prequalified generic manufacturer of this product.²⁹

Patents

Generic companies in India were able to develop this co-pack because patents on the individual components contained in the combination did not exist.

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



TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE (TDF/FTC)

GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI in a double fixed-dose combination.
- 2010 WHO guidelines: Indicated for first-line and second-line treatment for adults and adolescents.¹³ For adolescents more than 12 years of age with hepatitis B, the preferred regimen is TDF/FTC or lamivudine (3TC) and NNRTI.²⁹
- Originator company and product brand name: Gilead, Truvada.
- First approved by US Food and Drug Administration (FDA): August 2004.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults.³¹ 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.³¹
- World sales of originator product: 2011: US\$2.87 billion; 2010: \$2.65 billion; 2009: \$2.49 billion; 2008: \$2.11 billion; 2007: \$1.59 billion; 2006: \$1.19 billion; 2005: \$568 million; 2004: \$68 million.^{128,129,130,133}
- Patents: Most patents related to TDF or to FTC also affect this combination. Gilead applied for patents related specifically to this combination in 2004 which are due to expire in 2024.²⁵³

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 June 2012) are in **bold**.

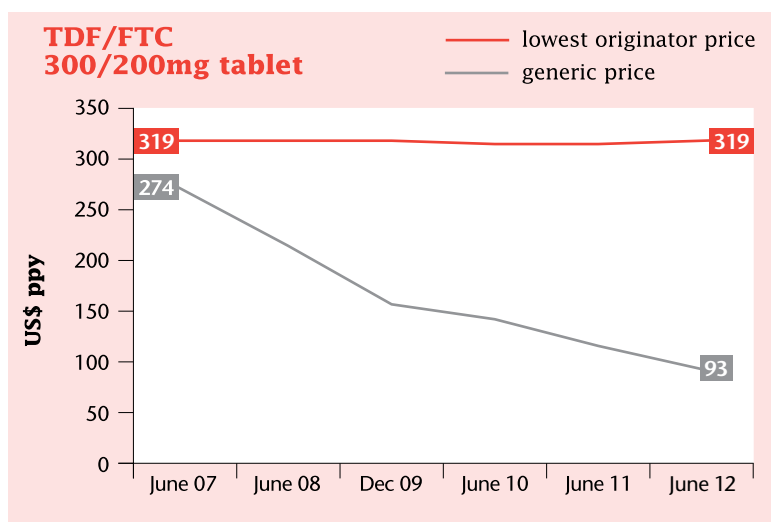
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	Gilead		Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy
		Category 1 countries	Category 2 countries					
TDF/FTC 300/200mg tablet	1	319 (0.875)	548 (1.500)	100 (0.275)	108 (0.297)	93 (0.255)	97 (0.267)	103 (0.283)

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

As of June 2012, there are several generic sources of TDF/FTC 300/200mg tablet which are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2007, the generic price has decreased 66%. The originator price has remained constant, but is reserved for low-income countries (see Annex 2).



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

According to the WHO treatment guidelines, 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.^{13,29} This means this formulation is interchangeable with TDF/3TC.

There are several WHO-prequalified generic sources of this product –

their price has fallen in the past year, from US\$116 ppy at best in 2011, to between \$93 and \$108 today.

Paediatrics

In January 2012, the US FDA approved Gilead's TDF for use in patients above the age of two.²⁵² Approved formulations are a 40mg/gr of oral powder and 150mg, 200mg, 250mg and 300mg tablets.

The approval of TDF use in children is a step forward as it opens up the possibility of aligning first-line ART for adults and children over three.^{29,229} This would simplify treatment options for all and potentially simplify drug procurement for HIV programmes.

Patents

Patents on TDF/FTC exist in Brazil, China and in ARIPO countries.⁴⁷

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

For 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 refer to the TDF drug profile. Additional information is also available on the FTC drug profile.

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

GENERAL INFORMATION

- Therapeutic class: One NtRTI, one NRTI and one NNRTI in a triple fixed-dose combination.
- 2010 WHO guidelines: Indicated for first-line treatment for adults and adolescents.¹³ For adolescents more than 12 years of age with hepatitis B, the preferred regimen is TDF/FTC or lamivudine (3TC) and NNRTI.²⁹
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb (BMS)/Merck, Atripla.
- First approved by US Food and Drug Administration (FDA): July 2006.³⁰
- WHO Model List of Essential Medicines (EML): This FDC is included in the 17th edition for adults.³¹ 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.³¹
- World sales of the originator: 2011: US\$3.22 billion; 2010: \$2.927 billion; 2009: \$2.382 billion; 2008: \$1.572 billion; 2007: \$903 million; 2006: \$164 million (the product entered the market in the third quarter of the year).^{128,129,133}
- 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 2006,²⁸⁰ which would last until 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 June 2012) are in **bold**.

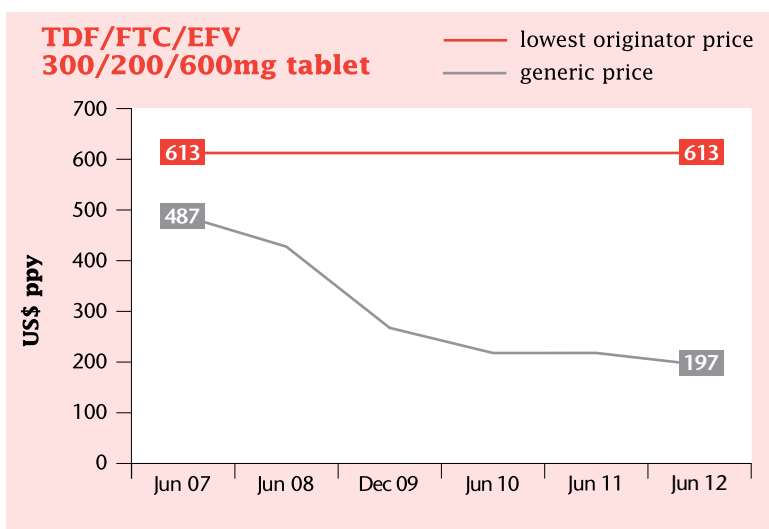
Please refer to Annex 2 for the conditions of eligibility set by individual companies, as well as for the incoterms associated with these prices.

	Daily dose	Merck		Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy
		Category 1 countries	Category 2 countries					
TDF/FTC/EFV 300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	183 (0.500)	207 (0.567)	140 (0.383)	197 (0.540)	100 (0.275)

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

As of June 2012, there are two generic sources of TDF/FTC/EFV 300/200/600mg tablet which 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 60%.



SPOTLIGHT ON ACCESS ISSUES

This is a one-pill-a-day FDC, which makes it well-adapted to resource-poor settings.

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

According to the WHO treatment guidelines, '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'. This means this formulation is interchangeable with TDF/3TC/EFV.^{13,29}

There are currently two WHO-prequalified generic sources of TDF/FTC/EFV, and one WHO-prequalified source of TDF/3TC/EFV. This year the lowest WHO-prequalified generic price for this product is US\$197, down from \$219 in 2011. This is still higher than the lowest reported price for TDF/3TC/EFV (\$172).

Based on WHO 2010 treatment guidelines for adults and adolescents, NVP was preferred over EFV, as a first-line treatment option

for pregnant women.²⁹ Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as part of a simplified first-line treatment including among pregnant women and those of reproductive age.²⁸¹

Paediatrics

In January 2012, the US FDA approved Gilead's TDF for use in patients above the age of two.²⁵² Approved formulations are a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

The approval of TDF use in children is a step forward as it opens up the possibility of aligning first-line ART for adults and children over three.^{29,229} This would simplify treatment options for all and potentially simplify drug procurement for HIV programmes.

Patents

In July 2006, the originator version of TDF/FTC/EFV (marketed as 'Atripla') became the first multi-class antiretroviral drug approved by the US FDA. It was also the first collaboration between two US pharmaceutical companies combining patented HIV medicines into one product, as Gilead's TDF and FTC are combined with Bristol-Myers Squibb's EFV.²⁸² Atripla is

marketed in North America and Europe jointly by Gilead and BMS but in much of the developing world, marketing and distribution is handled by Merck.²⁸³

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead²⁸⁴ and BMS²⁸⁵ have applied for patents related to TDF, including the one specifically related to this combination.²⁸⁶ If these patents are granted in India, generic competition for this product may be affected.

In addition, given the limitations of Gilead's voluntary licencing in India, countries not covered under these licences may face barriers in procuring TDF/FTC/EFV from the Indian manufacturers producing this FDC outside of the voluntary licence arrangements.

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, as well as the Brazilian initiative for local production, please refer to the TDF drug profile. Additional information is also available on the FTC and EFV drug profiles.



TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI in a double fixed-dose combination.
- 2010 WHO guidelines: Indicated for first- and second-line treatment for adults and adolescents.¹³
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults; 3TC is also included in the 3rd edition for children.^{31,32} 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.³¹
- Patents: Patents related to TDF or to 3TC also affect this combination. Other patents may have been applied for, more specifically related to this fixed-dose combination, including one by Cipla.²⁸⁷

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 June 2012) 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.

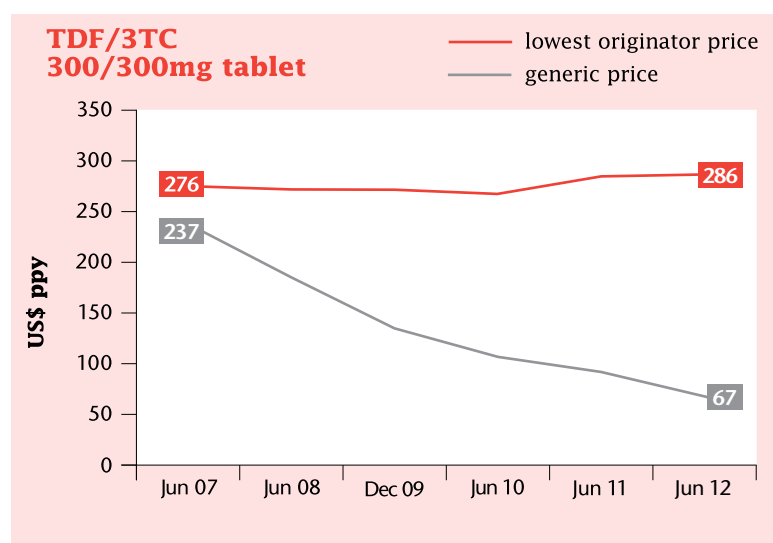
	Daily dose	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy
TDF/3TC 300/300mg tablet	1	88 (0.242)	80 (0.220)	69 (0.188)	67 (0.183)	40 (0.109)

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

As of June 2012, there are four generic sources of TDF/3TC 300/300mg tablet which 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 2007, the combined originator price of the two individual products has increased by 3% whereas the generic price has decreased by 71%. The most affordable generic FDC is 76% less expensive than the sum of the originator products.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

According to the WHO treatment guidelines, 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.^{13,29} This means this formulation is interchangeable with TDF/FTC.

The lowest WHO-prequalified generic source, at US\$67 ppy, is priced substantially more affordably than the lowest WHO-prequalified generic source of TDF/FTC (\$93).

Paediatrics

In January 2012, the US FDA approved Gilead's TDF for use in patients above the age of two.²⁵² Approved formulations are a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

The approval of TDF use in children is a step forward as it opens up the possibility of aligning first-line ART for adults and children over three.^{29,229} This would simplify treatment options for all and potentially simplify drug procurement for HIV programmes.

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.^{29,229}

Patents

There is no originator TDF/3TC FDC.

This combination is produced by Indian generic companies because neither of the individual components is patented in India. 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.

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, as well as the Brazilian initiative for local production, please refer to the TDF drug profile. Additional information is also available on the 3TC drug profile.



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

GENERAL INFORMATION

- Therapeutic class: One NtRTI, one NRTI and one NNRTI in a triple fixed-dose combination.
- 2010 WHO guidelines: Indicated for first-line treatment for adults and adolescents.¹³ For adolescents more than 12 years of age with hepatitis B, the preferred regimen is TDF/emtricitabine (FTC) or 3TC and NNRTI.²⁹
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults.³¹ 3TC and EFV are also included in the 3rd edition for children.³² 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.³¹
- Patents: Patents related to TDF, 3TC and to EFV also affect this combination. Other patents specifically related to this specific 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 June 2012) 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.

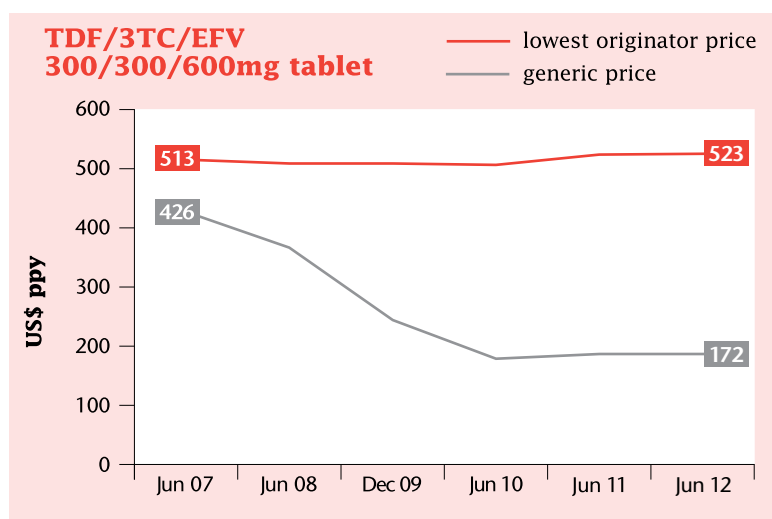
	Daily dose	Matrix (Mylan)	Hetero
TDF/3TC/EFV 300/300/600mg tablet	1	172 (0.470)	128 (0.350)

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

As of June 2012, there is still only one generic source of TDF/3TC/EFV 300/300/600mg tablet which is quality-assured by US FDA or WHO prequalification.

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 60%. The combined originator price of the three individual products has increased by 2%.



SPOTLIGHT ON ACCESS ISSUES

This is a one-pill-a-day fixed-dose combination (FDC), which makes it well-adapted to resource-poor settings.

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

According to the WHO treatment guidelines, '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'.^{13,29} This means this formulation is interchangeable with TDF/FTC/EFV.

As of June 2012, there is still only one WHO-prequalified source of TDF/3TC/EFV, which at US\$172 ppy, is priced more affordably than the WHO-prequalified generic TDF/FTC/EFV (\$197). This monopolistic

situation has prevented any downward trend in prices. However, it is expected that several companies will have their products approved by US FDA and/or WHO prequalification in the coming months. If this occurs, the price of this formulation may drop significantly due to increased competition.

Based on WHO 2010 treatment guidelines for adults and adolescents, NVP was preferred over EFV, as a first-line treatment option for pregnant women.²⁹ Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as part of a simplified first-line treatment including among pregnant women and those of reproductive age.²⁸¹

Paediatrics

In January 2012, the US FDA approved Gilead's TDF for use in patients above the age of two.²⁵² Approved formulations are a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets.

The approval of TDF use in children is a step forward as it opens up the possibility of aligning first-line ART for adults and children over three.^{29,229} This would simplify treatment options for all and potentially simplify drug procurement for HIV programmes.

Patents

There is no originator TDF/3TC/EFV FDC.

This combination is produced by Indian generic companies because none of the individual components is patented in India. 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.

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, as well as the Brazilian initiative for local production, please refer to the TDF drug profile. Additional information is also available on the 3TC and EFV drug profiles.

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



GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI (in a double fixed-dose combination) with one NNRTI in a co-pack.
- 2010 WHO guidelines: Indicated for first-line treatment for adults and adolescents.¹³
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults.³¹ 3TC and NVP are included in the 3rd edition for children.³² 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.³¹
- 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 June 2012) 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	Matrix (Mylan)
TDF/3TC + NVP 300/300 + 200mg tablets (co-pack)	1 kit (2 tablets)	122 (0.333)

SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

Based on WHO 2010 treatment guidelines for adults and

adolescents, NVP was preferred over EFV, as a first-line treatment option for pregnant women.²⁹ Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as part of a simplified first-line treatment including among pregnant women and those of reproductive age.²⁸¹

This product is a co-pack and comes with a higher pill burden

than existing FDCs, such as TDF/3TC/EFV or TDF/FTC/EFV.^{281, 288}

This factor, along with the emerging evidence around the safety of EFV in pregnant women, make it a less preferable option.

Patents

Please refer to the TDF, 3TC and NVP drug profiles.



TENOFOVIR DISOPROXIL FUMARATE/ LAMIVUDINE + ATAZANAVIR + RITONAVIR (TDF/3TC + ATV + r)

GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI (in a double fixed-dose combination), with one boosted protease inhibitor in a co-pack.
- 2010 WHO guidelines: Indicated for second-line treatment for adults and adolescents.¹³
- Originator company and product brand name: No originator product exists
- First approved by US Food and Drug Administration (FDA): Not applicable
- WHO Model List of Essential Medicines (EML): Individual medicines are included in the 17th edition for adults.³¹ 3TC, ATV and RTV are also included in the 3rd edition for children.³² 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.³¹
- Patents: Patents related to TDF, 3TC, ATV and RTV 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 June 2012) 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	Matrix (Mylan)
TDF/3TC + ATV + r 300/300 + 300 + 100mg tablets (co-pack)	1 kit (3 tablets)	365 (1.000)

SPOTLIGHT ON ACCESS ISSUES

This combination can be used as second-line therapy, if TDF was not already used in a first-line regimen.

It is available as a co-pack of three pills. With the recent introduction of an ATV/r FDC, there is the potential for this regimen to be developed in a co-pack of only two pills in the future.

Please see the TDF/3TC and the ATV/r drug profiles for more information.

At US\$371 ppy, this co-pack is priced similarly to the sum of the TDF/3TC FDC (\$67) and ATV/r FDC (US\$304 PPY).

Patents

Please refer to individual TDF, 3TC, ATV and RTV drug profiles.

ZIDOVUDINE/ LAMIVUDINE (AZT/3TC)

GENERAL INFORMATION

- Therapeutic class: Two NRTIs in a double fixed-dose combination.
- 2010 WHO Guidelines: Indicated for first- and second-line treatment for adults, adolescents and children.^{13,29}
- 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 1997.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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.³¹
- World sales of the originator: 2011: US\$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.^{33,34,35,36,37,38,154,155}
- 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,²⁸⁹ and for the tablet formulation of the fixed-dose combination,²⁹⁰ which are due to expire in 2012 and 2017, respectively.

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of June 2012) 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	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Universal Corporation	Varichem
AZT/3TC 60/30mg tablet (paediatrics)	4		79 (0.054)	78 (0.053)		67 (0.046)			73 (0.050)**		
AZT/3TC 300/150mg tablet	2	386 (0.529)	103 (0.141)	103 (0.141)	100 (0.137)	96 (0.132)	95 (0.131)	151 (0.206)	103 (0.141)	96 (0.132)	107 (0.147)

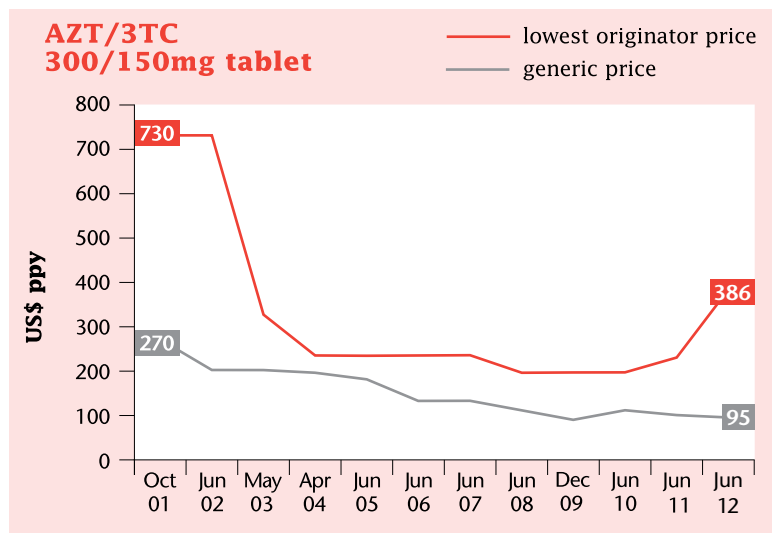
**This formulation is dispersible.

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

As of June 2012, nine 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 47% while the generic price has dropped by 65%.

However, it should be noted that the price of the innovator has increased by 40%, compared to last year and this price is reserved for low-income countries, least-developed countries and sub-Saharan Africa.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³ AZT is also recommended for second-line treatment if TDF has been used in first-line regimen.¹³

Based on WHO guidelines, TDF is preferred over AZT if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.

There are several WHO-prequalified generic sources of the 300/150mg tablet.

The 300/150mg formulations continue to have a role in PMTCT programmes in developing countries.²⁰¹

Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT as the preferred NRTI to be given with 3TC and either an NNRTI or a PI in the first line. AZT can also be part of second-line regimens, depending on what has been used as a first line.²⁹

Toxicity risks are associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.²⁹

There are now four WHO-prequalified generic sources of the 60/30mg tablet (up from two last year), of which one is dispersible. The lowest reported price this year is US\$67, compared to \$73 last year.

Patents

This combination was produced by Indian generic companies because none of the individual components were patented in India. However, these generic versions came under

threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination.^{291,292} Civil society organisations in India opposed the patent application in March 2006,²⁹³ which resulted in GSK announcing the withdrawal in all countries of all patent applications specifically related to the fixed-dose combination, in August 2006.²⁹⁴

In China, a patent on 3TC expired in 2011. The generic version of 3TC has completely replaced ViiV's product in the national free ART programme. Anhui began production of generic AZT/3TC in 2011, and the generic version of the FDC will be available in the national ART programme from the second half of 2012. However, for paediatric patients, the programme still relies on the ViiV product.

In some countries, generic versions of the FDC are not available because of GSK patent rights. AZT/3TC patents exist in ARIPO and OAPI countries,⁴⁷ which could prevent the importation and use of this combination.

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

GENERAL INFORMATION

- Therapeutic class: Three NRTIs in a triple fixed-dose combination.
- 2010 WHO guidelines: This regimen is recommended for treatment for individuals who are unable to tolerate or have contra-indications to NNRTI-based regimens, particularly in the following situations: HIV/TB co-infection, pregnant women, chronic viral hepatitis B and HIV-2 infection.¹³ This triple NRTI regimen can be used to simplify management of toxicity, co-morbidity and drug-drug interactions.²⁹ This triple NRTI regimen is recommended in infants and children who are HIV/TB co-infected and are on a rifampicin-containing regimen for the treatment of TB.
- 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 2000.³⁰
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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.³¹
- World sales of originator product: 2011: US\$204 million; 2010: \$233 million; 2009: \$307 million; 2008: \$350 million; 2007: \$455 million; 2006: \$529 million; 2005: \$598 million; 2004: \$635 million.^{33,34,35,36,37,38,154,155}
- Patents: Patents on AZT, 3TC, AZT/3TC or ABC also affect this combination. GSK applied for patents more specifically related to the triple combination.²⁷⁸

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 June 2012) are in **bold**.

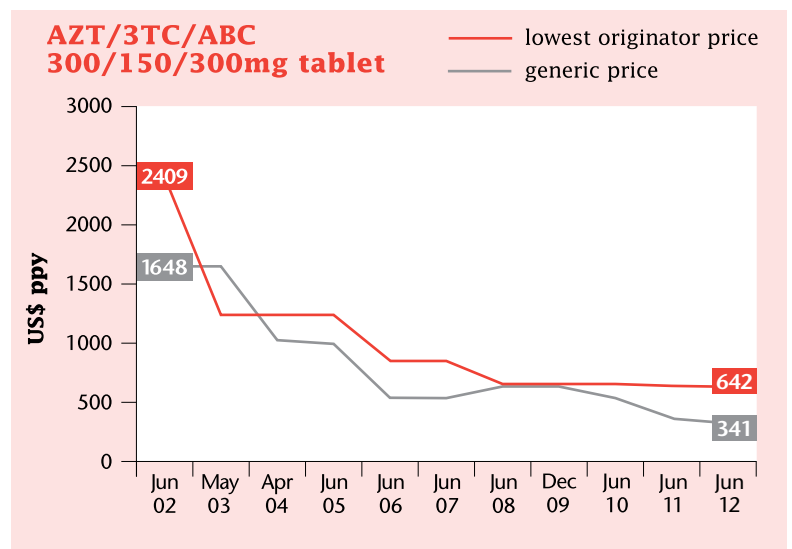
Please refer to Annex 2 for the conditions of eligibility set by individual companies, and for the incoterms associated with these prices.

	Daily dose	ViiV	Matrix (Mylan)	Ranbaxy
AZT/3TC/ABC 300/150/300mg tablet	2	642 (0.879)	341 (0.467)	371 (0.508)

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

As of June 2012, there are two generic sources of AZT/3TC/ABC 300/150/300mg tablet that are quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2002, the originator price has decreased by 73% and the generic price has dropped by 79%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).

This FDC 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. This formulation is indicated as key in the WHO antiretroviral guidelines particularly for people co-infected with TB/HIV, pregnant women, patients with chronic viral hepatitis and those with HIV-2 infection.¹³

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

Paediatrics

This regimen is one of the two recommended first-line regimens in children aged two years and above. WHO also recommends AZT/3TC/ABC as an option for TB/HIV co-infected paediatric patients.²⁹

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

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 Indian generic companies to develop generic versions of each medicine and of the combination. However, these generic versions came under threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination. Civil society organisations in India opposed the patent application in March 2006, which resulted in GSK announcing the withdrawal in all countries of all patent applications specifically related to the fixed-dose combination, in August 2006.²⁹⁶

Please refer to the ABC, AZT and 3TC drug profiles for further information.



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

GENERAL INFORMATION

- Therapeutic class: Two NRTIs and one NNRTI in a triple fixed-dose combination.
- 2010 WHO guidelines: Indicated for first-line treatment for adults, adolescents and children.^{13,29}
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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.³¹
- 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 June 2012) are in **bold**.

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

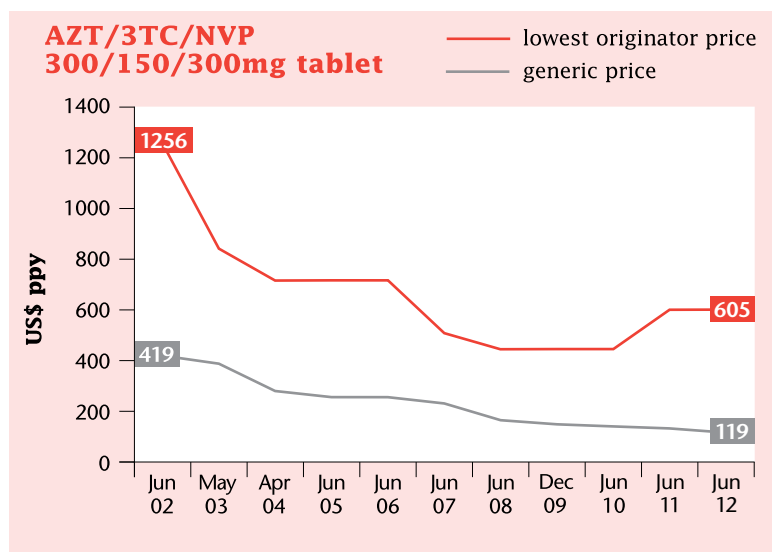
	Daily dose	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Quality Chemicals	Ranbaxy
AZT/3TC/NVP 60/30/50mg tablet (paediatrics)	4				101 (0.069)		
AZT/3TC/NVP 300/150/200mg tablet	2	134 (0.183)	124 (0.170)	119 (0.164)	134 (0.183)	176 (0.242)	127 (0.174)

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

As of June 2012, there are six generic sources of AZT/3TC/NVP 300/150/200mg tablet which 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 fixed-dose combination of AZT/3TC and nevirapine single formulation.

Since 2002, the originator price has decreased by 52% whereas the generic price has dropped by 71%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³

Based on WHO 2010 treatment guidelines for adults and adolescents, NVP was preferred over EFV, as a first-line treatment option for pregnant women.²⁹ Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as past of a simplified first-line treatment including among pregnant women and those of reproductive age.²⁸¹

Paediatrics

According to WHO 2010 treatment guidelines for infants and children, this regimen is recommended as first-line treatment for infants and children not previously exposed to NNRTIs.²⁹

HIV/TB co-infected young children cannot be given NVP because of interactions between NVP and TB drugs.

There is only one WHO-prequalified generic source for the paediatric 60/30/50mg tablet.

Patents

There is no originator AZT/3TC/NVP FDC.

In early 2004, at a time when no generic versions of the FDC were available, MSF approached Canadian generic company Apotex to develop the FDC, 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.²⁹⁹

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.²⁹⁸

Apotex did manufacture an AZT/3TC/NVP FDC, 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 2009.²⁹⁷ In the meantime, the FDC 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 members should reform the mechanism, as it is far from providing an adequate solution to the needs to developing countries without manufacturing capacity.

Please refer to the AZT, 3TC and NVP drug profiles for further information.

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

GENERAL INFORMATION

- Therapeutic class: Two NRTIs (in a double fixed-dose combination), with one NNRTI in a co-pack.
- 2010 WHO guidelines: Indicated for first-line treatment for adults, adolescents and children.^{13,29}
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition for adults and the 3rd edition for children.^{31,32} 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.³¹
- 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.²⁹⁵

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 June 2012) 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.

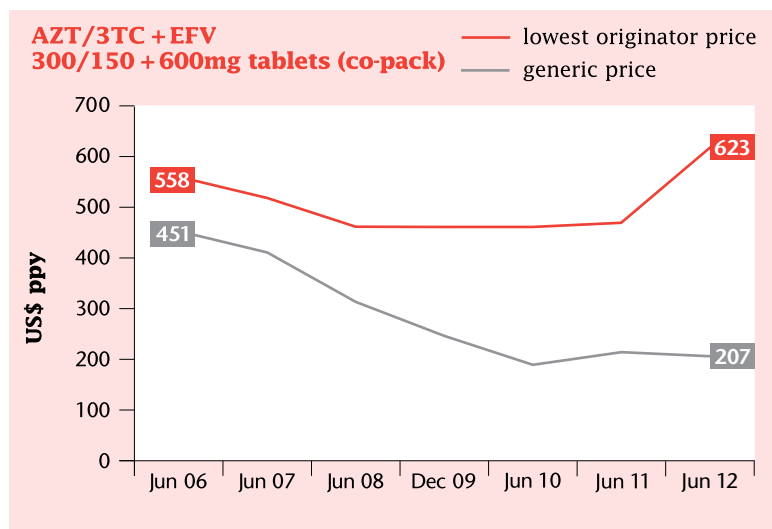
	Daily dose	Aurobindo	Ranbaxy
AZT/3TC + EFV 300/150 + 600mg tablets (co-pack)	1 kit (2 tablets)	207 (0.567)	231 (0.633)

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

As of June 2012, there are three generic sources of AZT/3TC + EFV 300/150 + 600mg tablets (co-pack) that are quality-assured by US FDA or WHO prequalification, but only two of the companies have provided pricing information for this year's publication. 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 fixed-dose combination of AZT/3TC and efavirenz single formulation.

Since 2006, the generic price has decreased by 54%. Since 2011, the originator price has increased by 25%.



SPOTLIGHT ON ACCESS ISSUES

WHO has advised countries to phase out stavudine (d4T)-based regimens because of their long-term irreversible side effects. Instead, zidovudine (AZT) or tenofovir-based (TDF) first-line regimens should be used, together with either lamivudine (3TC) or emtricitabine (FTC) and either efavirenz (EFV) or nevirapine (NVP).¹³ AZT is also recommended for second-line treatment if tenofovir has been used in first-line regimen.¹³

Based on WHO guidelines, TDF is preferred over AZT if a patient is at increased risk of developing bone marrow suppression (anaemia or neutropenia), which is a major side effect of AZT.

Based on WHO 2010 treatment guidelines for adults and adolescents, NVP was preferred over EFV, as a first-line treatment option for pregnant women.²⁹ Recent WHO advice highlights the programmatic consequences of avoiding EFV use in pregnancy and supported its use as part of

a simplified first-line treatment including among pregnant women and those of reproductive age.²⁸¹

No FDC is available for this regimen.

Paediatrics

EFV is indicated only in children above three years of age.

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line treatment. The combination can also be part of second-line regimens, depending on what has been used as first line.²⁹

Toxicity risks are associated with AZT, with possible anaemia developing over the first few months of therapy but the drug remains much better tolerated than d4T.²⁹ For children co-infected with tuberculosis and above the age of three, the preferred regimen is EFV and two NRTIs.²⁹

Currently a co-pack of AZT/3TC + EFV for children does not exist. Please refer to AZT/3TC and 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 develop this co-pack.

AZT/3TC patents exist in ARIPO and OAPI countries⁴⁷ which could prevent the importation and use of this combination.

Please refer to the EFV, 3TC and AZT drug profiles for further information.

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 June 2012) 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	Matrix (Mylan)	Ranbaxy	Strides		
20mg/ml oral solution	12 ml	415 (0.095/ml)		183 (0.042/ml)	256 (0.058/ml)	210 (0.048/ml)	160 (0.036/ml)					
60mg tablet	4				134 (0.092)	170 (0.117)		122 (0.083)				
300mg tablet	2	380 (0.520)			183 (0.250)	243 (0.333)	169 (0.232)	170 (0.233)	237 (0.325)	256 (0.350)		
Atazanavir (ATV)*		BMS		Emcure	Hetero	Matrix (Mylan)						
		Category 1 countries	Category 2 countries									
100mg capsule	xx			(0.267)								
150mg capsule	2	412 (0.564)	361 (0.495)	268 (0.367)								
200mg capsule	xx	(0.677)	(0.594)	(0.483)								
300mg capsule	1			268 (0.733)	280 (0.767)	231 (0.633)						
Atazanavir/ritonavir (ATV/r)				Matrix (Mylan)								
300/100mg tablet	1			304 (0.833)								
Darunavir (DRV)*		Janssen (J&J)		Hetero								
300mg tablet	4	803 (0.550)										
400mg tablet				730 (1.000)								
600mg tablet				1095 (1.500)								
Didanosine (ddl)		BMS		Aurobindo	Matrix (Mylan)	Ranbaxy						
		Category 1 countries	Category 2 countries									
2g powder for reconstitution (final concentration 10mg/ml)	12ml	233 (12.590/2g)	case-by-case basis									
25mg tablet	6	256 (0.117)	case-by-case basis			402 (0.183)						
50mg tablet	xx	(0.158)	case-by-case basis			(0.217)						
100mg tablet	xx	(0.213)	case-by-case basis	(0.133)		(0.250)						
150mg tablet	xx			(0.200)								
200mg tablet	xx			(0.258)								
125mg enteric-coated capsule	1			110 (0.300)	119 (0.325)							
200mg enteric-coated capsule	xx			(0.400)	(0.471)							
250mg enteric-coated capsule	1	223 (0.611)	277 (0.758)	170 (0.467)	180 (0.492)	(0.484)						
400mg enteric-coated capsule	1	288 (0.789)	357 (0.978)	256 (0.700)	267 (0.733)	243 (0.665)						

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

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies									
Efavirenz (EFV)		Merck		Aspen	Aurobindo	Cipla	Emcure	Hetero	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Strides
		Category 1 countries	Category 2 countries										
30mg/ml oral solution	xx	(0.094/ml)	case-by-case basis										
50mg capsule	xx				(0.082)					(0.072)			
50mg tablet	xx	(0.120)	case-by-case basis										
100mg dispersible tablet	xx											(0.150)	
200mg capsule	3				91 (0.083)	146 (0.133)				61 (0.056)		82 (0.075)	
200mg tablet	3	394 (0.360)	case-by-case basis										113 (0.103)
600mg tablet	1	237 (0.650)	case-by-case basis	62 (0.170)	61 (0.167)	66 (0.180)	61 (0.167)	53 (0.145)	49 (0.133)	44 (0.120)	97 (0.265)	56 (0.153)	46 (0.125)
Emtricitabine (FTC)				Aurobindo	Cipla								
200mg capsule	1			58 (0.158)	85 (0.233)								
Etravirine (ETV)		Janssen (J&J)											
100mg tablet	4	438 (0.300)											
Fosamprenavir (FPV)*		ViiV											
50mg/ml suspension	12ml	783 (0.179/ml)											
700mg tablet	2	1125 (1.541)											
Indinavir (IDV)*		Merck		Aurobindo	Hetero								
		Category 1 countries	Category 2 countries										
400mg capsule	4	394 (0.270)	case-by-case basis	268 (0.183)	430 (0.294)								
Lamivudine (3TC)		ViiV		Alkem	Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Ranbaxy	Strides	
10mg/ml oral suspension	10ml	212 (0.058/ml)			34 (0.009/ml)	30 (0.008/ml)	40 (0.011/ml)						
150mg tablet	2	79 (0.109)		43 (0.058)	29 (0.040)	32 (0.044)	34 (0.047)	32 (0.044)	30 (0.042)	27 (0.037)	28 (0.038)	28 (0.038)	
300mg tablet	1					24 (0.067)	27 (0.075)			21 (0.058)			
Lopinavir/ritonavir (LPV/r)		Abbott		Aurobindo	Cipla	Hetero	Matrix (Mylan)						
		Category 1 countries	Category 2 countries										
80/20mg/ml oral solution	4ml	147 (0.101/ml)	296 (0.203/ml)										
100/25mg heat-stable tablet	3	138 (0.126)	278 (0.254)	164 (0.150)			164 (0.150)						
200/50mg heat-stable tablet	4	368 (0.252)	740 (0.507)	402 (0.275)	481 (0.329)	389 (0.267)	371 (0.254)						

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

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies										
		Category 1 countries	Category 2 countries	Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Strides	Universal Corporation	
Nevirapine (NVP)		Boehringer Ingelheim												
10mg/ml suspension	20ml	380 (0.052/ml)	532 (0.073/ml)		64 (0.009/ml)	117 (0.016/ml)								
50mg tablet for oral suspension	4				66 (0.045)									
200mg capsule	2													30 (0.041)
200mg tablet	2	219 (0.300)	438 (0.600)	37 (0.051)	35 (0.048)	38 (0.052)	34 (0.047)	33 (0.046)	29 (0.040)	48 (0.066)	32 (0.044)	29 (0.040)		
Raltegravir (RAL)		Merck												
400mg tablet	2	675 (0.925)	case-by-case basis											
Ritonavir (RTV)		Abbott		Matrix (Mylan)										
80mg/ml oral solution	xx	(0.091/ml)	case-by-case basis											
100mg heat-stable tablet	2	83 (0.114)	case-by-case basis	178 (0.243)										
Saquinavir (SQV)*		Roche												
200mg hard capsule	10	1489 (0.408)	2981 (0.817)											
500mg tablet	4	1366 (0.935)	2978 (2.040)											
Stavudine (d4T)		BMS		Aspen	Aurobindo	Cipla	Ranbaxy	Strides						
1mg/ml powder for oral solution	20ml	55 (0.008/ml)	case-by-case basis		55 (0.008/ml)	68 (0.009/ml)								
15mg capsule	xx			(0.027)	(0.025)									
20mg capsule	xx		(0.103)	(0.031)	(0.027)									
30mg capsule	2		75 (0.103)		21 (0.028)		30 (0.042)	19 (0.027)						
40mg capsule	2		75 (0.103)											
Tenofovir (TDF)		Gilead		Aspen	Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy	Strides				
300mg tablet	1	207 (0.567)	365 (1.000)	87 (0.237)	73 (0.200)	67 (0.183)	59 (0.162)	64 (0.175)	60 (0.165)	57 (0.157)				
Zidovudine (AZT)		ViiV		Aspen	Aurobindo	Cipla	Hetero	Micro Labs	Matrix (Mylan)	Ranbaxy				
10mg/ml oral solution	24ml	377 (0.043/ml)									107 (0.012/ml)	82 (0.009/ml)	106 (0.012/ml)	
60mg tablet	4											73 (0.050/ml)		
100mg capsule	xx	(0.184)			(0.048)	(0.055)								
100mg tablet	xx											(0.065)		
250mg capsule	xx	(0.299)												
300mg tablet	2			100 (0.136)	85 (0.117)	85 (0.117)	83 (0.114)	82 (0.112)	82 (0.112)	75 (0.103)				

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

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies									
ABC/3TC		ViiV		Aurobindo	Cipla	Matrix (Mylan)							
60/30mg tablet	4			164 (0.113)	175 (0.120)	140 (0.096)							
600/300mg tablet	1	230 (0.629)		213 (0.583)	389 (1.067)	268 (0.733)							
3TC/d4T				Cipla	Hetero	Matrix (Mylan)	Ranbaxy	Strides					
30/6mg dispersible tablet	4			46 (0.032)									
60/12mg dispersible tablet	2			40 (0.055)									
150/30mg tablet	2			40 (0.055)	39 (0.053)	37 (0.050)	39 (0.053)	36 (0.049)					
3TC/d4T + EFV (co-pack)				Strides									
150/30 + 600mg (co-pack)	1 kit (2 tabs)			213 (0.583)									
3TC/d4T/NVP				Cipla	Hetero	Ranbaxy	Strides	Varichem					
30/6/50mg dispersible tablet	4			56 (0.038)									
60/12/100mg dispersible tablet	2			52 (0.072)									
150/30/200mg tablet	2			61 (0.083)	61 (0.083)	62 (0.085)	56 (0.077)	61 (0.083)					
TDF/FTC		Gilead		Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy					
		Category 1 countries	Category 2 countries										
300/200mg tablet	1	319 (0.875)	548 (1.500)	100 (0.275)	108 (0.297)	93 (0.255)	97 (0.267)	103 (0.283)					
TDF/FTC/EFV		Merck		Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy					
		Category 1 countries	Category 2 countries										
300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	183 (0.500)	207 (0.567)	140 (0.383)	197 (0.540)	100 (0.275)					
TDF/3TC				Aurobindo	Cipla	Hetero	Matrix (Mylan)	Ranbaxy					
300/300mg tablet	1			88 (0.242)	80 (0.220)	69 (0.188)	67 (0.183)	40 (0.109)					
TDF/3TC/EFV				Matrix (Mylan)	Hetero								
300/300/600mg tablet	1			172 (0.470)	128 (0.350)								
TDF/3TC + EFV (co-pack)				Hetero									
300/300 + 600mg co-pack	1 kit (2 tabs)			128 (0.350)									
TDF/3TC + NVP (co-pack)				Matrix (Mylan)									
300/300 + 200mg co-pack	1 kit (2 tabs)			122 (0.333)									
TDF/3TC + ATV + r (co-pack)				Matrix (Mylan)									
300/300 + 300mg + 100mg co-pack	1 kit (3 tabs)			365 (1.000)									
AZT/3TC		ViiV		Aurobindo	Cipla	Hetero	Matrix (Mylan)	Micro Labs	Quality Chemicals	Ranbaxy	Universal Corporation	Varichem	
60/30mg tablet	4			79 (0.054)	78 (0.053)		67 (0.046)			73 (0.050)			
300/150mg tablet	2	386 (0.529)		103 (0.141)	103 (0.141)	100 (0.137)	96 (0.132)	95 (0.131)	151 (0.206)	103 (0.141)	96 (0.132)	107 (0.147)	
AZT/3TC + EFV (co-pack)				Aurobindo	Ranbaxy								
150/300 + 600mg co-pack	1 kit (2 tabs)			207 (0.567)	231 (0.633)								
AZT/3TC/ABC		ViiV		Matrix (Mylan)	Ranbaxy								
300/150/300mg tablet	2	642 (0.879)		341 (0.467)	371 (0.508)								
AZT/3TC/NVP				Aurobindo	Cipla	Hetero	Matrix (Mylan)	Quality Chemicals	Ranbaxy				
60/30/50mg tablet	4						101 (0.069)						
300/150/200mg tablet	2			134 (0.183)	124 (0.170)	119 (0.164)	134 (0.183)	176 (0.242)	127 (0.174)				

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 specified.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Abbott	<p>Category 1 countries: Abbott includes in Category 1 all African countries and least-developed countries outside Africa. The following list was provided by Abbott:</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; South Sudan; Sudan; Swaziland; Tanzania; Timor-Leste; Togo; Tunisia; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.</p> <p>Category 2 countries: The following list was provided by Abbott:</p> <p>Albania; Armenia; Azerbaijan; Belarus; Bolivia; Bosnia-Herzegovina; Brazil; China; Colombia; Dominican Rep.; Ecuador; El Salvador; Fiji; Georgia; Guatemala; Guyana; Honduras; India; Indonesia; Jamaica; Jordan; Kazakhstan; Kyrgyzstan; FYR-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; Vietnam.</p>	Governments and programmes fully funded by governments, United Nations agencies, NGOs and other not-for-profit institutional treatment providers.		FCA Netherlands.
Alkem	No restrictions.	No restrictions.		FCA Mumbai.
Aspen	South African public sector only.	South African public sector only.		Ex-works.
Aurobindo	All countries except where patent restrictions and regulatory requirements prevent delivery.	No restrictions.	Orders should be minimum quantity. Freight and insurance are additional depending on incoterms (mode of shipment and destination).	Ex-works.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Boehringer Ingelheim (BI)	<p>Category 1 countries: BI includes in Category 1 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: 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; East Timor; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Kiribati; North Korea; Kyrgyzstan; 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; South Sudan; Sudan; Swaziland; Tajikistan; Tanzania; Togo; Tunisia; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.</p> <p>Category 2 countries: BI includes in Category 1 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: Albania; American Samoa; Antigua and Barbuda; Argentina; Armenia; Azerbaijan; Belarus; Belize; Bolivia; Bosnia-Herzegovina; Brazil; Bulgaria; Chile; China; Colombia; Costa Rica; Dominica; Dominican Rep.; Ecuador; Fiji; Georgia; Grenada; Guatemala; Guyana; Honduras; Indonesia; India; Iran; Iraq; Jamaica; Jordan; Kazakhstan; Kosovo; Latvia; Lebanon; Lithuania; FYR-Macedonia; Malaysia; Maldives; Marshall Islands; Mauritius; Mayotte; Mexico; Micronesia; Moldova; Mongolia; Montenegro; Nicaragua; Pakistan; Palau; Panama; Papua New Guinea; Paraguay; Peru; Philippines; Romania; Russia; Serbia; St Kitts and Nevis; St Lucia; St Vincent and the Grenadines; Sri Lanka; Suriname; Syria; Thailand; Timor-Leste; Tonga; Turkey; Turkmenistan; Ukraine; Uruguay; Uzbekistan; Venezuela; Vietnam; West Bank and Gaza.</p>	Governments, NGOs 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: BMS includes in Category 1 all sub-Saharan African countries (except Southern African countries), plus countries classified as low-income by the World Bank (except North Korea, Kyrgyzstan, Moldova and Uzbekistan). The following list was provided by BMS: 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; Vietnam; Yemen.</p> <p>Category 2 countries: BMS includes in Category 1 all Southern African countries). The following list was provided by BMS: 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 reported restrictions but higher prices have been negotiated separately for 10 Latin American countries.	No restrictions.	No quantity-related conditions. Prices for larger quantities are negotiable.	FOB Mumbai. Freight costs are charged separately.

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 antiretrovirals.	No restrictions.		Ex-works.
Gilead	<p>Category 1 countries: Gilead includes in Category 1, 108 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; Central African Republic; Chad; Comoros; Congo; Congo (DRC); Côte d'Ivoire; Cuba; Curacao; Djibouti; Dominica; Dominican Rep.; 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; 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.</p> <p>Category 2 countries: Gilead includes in Category 2, 12 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-Herzegovina; China; Ecuador; El Salvador; Fiji; Georgia; Iran; Iraq; Jordan; Kazakhstan; Kosovo; Montenegro; Panama; Paraguay; Peru; Philippines; Sri Lanka; Thailand; Tonga; Turkmenistan.</p> <p>For upper middle-income countries, prices are negotiated on a case-by-case basis.</p>			FOB Dublin.
Hetero	No restrictions.	Private sector, public sector and NGOs.	Prices may be negotiated on individual basis according to commercial terms.	FOB Mumbai.
Janssen (J&J)	<p>Janssen (J&J) includes in Category 1 all sub-Saharan Africa and least-developed countries outside of Africa. Based on this definition, and according to the classifications of least-developed countries by the United Nations, the following countries should be covered: Afghanistan; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (DRC); Côte d'Ivoire; Djibouti; East Timor; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Kiribati; Laos; Lesotho; Liberia; Madagascar; Malawi; Maldives; 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; Togo; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.</p> <p>For other low- and middle-income countries, differentiated prices are applicable and negotiated on a case-by-case basis.</p>	No restrictions.	Questions regarding supply in sub-Saharan Africa need to be addressed to Aspen.	FOB Johannesburg.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Matrix (Mylan)	<p>For tenofovir-based products – 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>For atazanavir – 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.
Merck	<p>For efavirenz, indinavir and raltegravir – Category 1 countries: Merck includes in Category 1 all countries in sub-Saharan Africa and low-income countries based on World Bank country classification. The following list was provided by Merck: Afghanistan; Angola; Bangladesh; Benin; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (DRC); Cote d'Ivoire; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; North Korea; Kyrgyzstan; Laos; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Rwanda; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Swaziland; Tajikistan; Tanzania; Togo; Uganda; Zambia; Zimbabwe.</p> <p>Category 2 countries: 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 pricing under this access programme.</p> <p>For TDF/FTC/EFV 300/200/600mg – Category 1 Countries: The following list was provided by Merck: 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 Rep.; 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>Category 2 countries: The following list was provided by Merck: Bolivia; Indonesia; Kyrgyzstan; Mauritius; Mongolia; Nicaragua; Seychelles; Syria; Tajikistan; Uzbekistan; Vietnam.</p>	<p>Category 1 countries: Governments and programmes fully funded by governments and/or by multi- and bi-lateral donors (i.e. the Global Fund, PEPFAR, or UNITAID), United Nations agencies, NGOs and other non-commercial providers of HIV treatment.</p> <p>Category 2 countries: Governments and programmes fully funded by governments and/or by multi- and bi-lateral donors (i.e. the Global Fund, PEPFAR, or UNITAID), United Nations agencies and NGOs.</p>	Additional costs may include freight, insurance, customs handling, taxes and duties.	CIP (port of entry).
Micro Labs	All countries except India.	All organisations and bodies except in India.		FCA Goa.
Quality Chemicals	No restrictions.	No restrictions.		FOB Kampala.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Ranbaxy	Ranbaxy offers the prices quoted to 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; Angola; Anguilla; Antigua and Barbuda; Argentina; Bahamas; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; Brazil; British Virgin Islands; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Chile; China; Colombia; Comoros; Congo (DRC); Côte d'Ivoire; Dominica; Dominican Rep.; Ecuador; El Salvador; Eritrea; Ethiopia; Gambia; Ghana; Grenada; Guatemala; Guinea; Guinea Bissau; Guyana; India; Haiti; Honduras; Indonesia; Jamaica; Kazakhstan; Kenya; North Korea; Kyrgyzstan; Laos; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritius; Montserrat; Morocco; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Pakistan; Panama; Papua New Guinea; Peru; Rwanda; St Kitts and Nevis; St Lucia; St Vincent and the Grenadines; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Somalia; South Africa; Sri Lanka; Suriname; Swaziland; Tajikistan; Tanzania; Thailand; Togo; Trinidad and Tobago; Turks and Caicos; Uganda; Ukraine; Vietnam; Zambia; Zimbabwe.	Ministries of Health and National AIDS control programmes, institutes affiliated with national health programmes, WHO, UNICEF, MSF, CHAI, PFSCM, IDA, PSI, and other NGOs receiving Global Fund grants.	All prices are indicative and vary depending on quantities ordered.	FOB Delhi.
Roche	<p>Category 1 countries: Roche includes in Category 1 all countries in sub-Saharan Africa and all least-developed countries. Based on this definition, and according to the classifications of least-developed countries by the United Nations, the following countries should be covered: Afghanistan; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo (DRC); Côte d'Ivoire; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Kiribati; 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; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.</p> <p>Category 2 countries: Roche includes in Category 2 low-income and lower middle-income countries. Based on this definition, and according to the classifications of low-income and lower middle-income economies by the World Bank, the following countries should be covered: Armenia; Belize; Bolivia; Egypt; El Salvador; Fiji; Georgia; Guatemala; Guyana; Honduras; India; Indonesia; Iraq; North Korea; Kosovo; Kyrgyzstan; Marshall Islands; Micronesia; Moldova; Mongolia; Morocco; Nicaragua; Pakistan; Papua New Guinea; Paraguay; Philippines; Sri Lanka; Syria; Tajikistan; Tonga; Turkmenistan; Ukraine; Uzbekistan; Vietnam; West Bank and Gaza.</p>	Governments, non-profit institutional providers of HIV care, NGOs.	CAD (Cash Against Documents/Cash on Delivery) 30 days at sight. Minimum order and delivery amount per shipment is CHF 10,000.	FCA Basel.
Strides Arcolab	No restrictions.	No restrictions.		FCA Chennai.
Universal Corporation	No restrictions.	No restrictions.		Ex-works.
Varichem	No restrictions.	No restrictions.	Prices depend on quantities ordered.	FOB Harare.
ViiV	ViiV includes in Category 1 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; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo (DRC); Côte d'Ivoire; Djibouti; East Timor; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Kiribati; North Korea; Kyrgyzstan; Laos; Lesotho; Liberia; Madagascar; Malawi; Maldives; 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; 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.

ANNEX 3: BARRIERS TO ACCESSING GENERICS – THE RESTRICTIONS POSED BY CERTAIN VOLUNTARY LICENCE AGREEMENTS

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 licencing arrangements between originator and generic producers. The following tableⁱ provides a non-exhaustive list of voluntary licences signed by different companies.

The claim is that such voluntary licences 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.

Nevertheless, a trend clearly emerges: that of originator companies limiting 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 in different licences ranges from 48 territories covered to 112.

Licences are often provided to a limited list of manufacturers. The table also reveals how voluntary licences are also signed covering drugs which are not patented, or where patents have expired in most of 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 licencing arrangements can therefore not be verified until companies to open their contractual terms and conditions for public scrutiny.

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
Abacavir (ABC)	GSK After Pfizer and GSK jointly announced the creation of a new joint venture on HIV medicines, all licences were transferred to ViiV.	Since 2009, ViiV has signed a licence agreement with the following company: Aspen	69 countries: sub-Saharan Africa + least-developed countries + low-income countries.	Non-exclusive licences. Detailed terms and conditions are confidential.
Atazanavir (ATV)	Bristol-Myers Squibb (BMS)	Since 2006, BMS signed licence agreements with the following companies: Aspen; Emcure; Mylan (Matrix); plus three other companies, names of which are unknown. In 2011 BMS announced a technology transfer agreement with the Brazilian Ministry of Health to manufacture ATV by Farmanguinhos (Fiocruz). The details of this agreement are not public.	48 countries: sub-Saharan Africa + India.	Royalty-free non-exclusive licences and immunity-from-suit agreements for manufacturing and distribution, including for paediatric formulations. Detailed terms and conditions are confidential.

i. Adapted from Peter Beyer, Developing socially responsible intellectual property licencing policies – non-exclusive licencing initiatives in the pharmaceutical sector in Jacques de Werra, Research Handbook on Intellectual Property Licencing, Edward Elgar Publishing, forthcoming 2012.

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
Cobicistat (COBI)	Gilead	<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-licences in India currently have signed agreements with the MPP: Emcure; Aurobindo; MedChem.</p> <p>In 2011, in a separate arrangement, Gilead also signed semi-exclusive licences for the supply of COBI with four Indian manufacturers:</p> <ul style="list-style-type: none"> • Matrix: for Sri Lanka, Thailand • Hetero and Ranbaxy: for Botswana, Namibia • Strides: for Ecuador, El Salvador, Indonesia, Kazakhstan, Turkmenistan. <p>In addition to these semi-exclusive territories, these 'preferred' licencees can also cover territories mentioned in Gilead-MPP licences. Detailed terms and conditions of these licences are confidential.</p>	<p>103 countries: Afghanistan; Angola, Anguilla, Antigua and Barbuda, Armenia, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Cuba, Djibouti, Dominica, Dominican Rep., Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Jamaica, Kenya, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Moldova, Mongolia, Montserrat, Mozambique, Myanmar, Nauru, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Palau, Papua New Guinea, Rwanda, St Kitts and Nevis, Saint Lucia, St Vincent and the Grenadines, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Suriname, Swaziland, Syria, Tajikistan, Tanzania, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe.</p>	<p>Non-exclusive licence granted to the Medicines Patent Pool, bearing a royalty of 5%, with no royalties on paediatric versions developed by licencees.</p> <p>The Gilead licences with the MPP are only the agreements where full terms are public. The licences carry an India-specific manufacturing restriction with further limitation on territories to which drugs can be supplied. Countries such as China, Brazil, Ukraine, Sri Lanka, and Indonesia are excluded.</p> <p>As a part of the 2011 semi-exclusive licences with four 'preferred' Indian generic manufacturers, Gilead will charge 10–15% royalties.</p>
Darunavir (DRV)	Janssen (Johnson & Johnson)	<p>Since 2007, Janssen (J&J) has signed licence agreements with the following companies: Aspen; Emcure.</p>	<p>65 countries: sub-Saharan Africa + least-developed countries + India.</p>	<p>Royalty-free non-exclusive licences.</p> <p>Aspen will register, package and distribute DRV at a differential price.</p> <p>Detailed terms and conditions are confidential.</p>
Didanosine (ddl)	Bristol-Myers Squibb (BMS)	<p>Since 2001, BMS signed licence agreements with the following companies: Adcock-Ingram; Aspen; Danpong-Adams; Enalenj; Sonke; Varichem; Thembalani; AfrikaBiopharm; Aurobindo; Emcure; Ranbaxy, Mylan (Matrix).</p>	<p>49 countries: sub-Saharan Africa + India.</p>	<p>11 immunity-from-suit agreements allowing generic companies to produce d4t and ddl. The agreements are royalty-free, include paediatric formulations.</p> <p>The agreements also cover stavudine.</p>
Efavirenz (EFV)	Merck	<p>Since 2007, Merck signed licence agreements with the following companies: Emcure; Arrow; Sonke; Aspen Aurobindo; Cipla-Medpro; Adcock Ingram.</p>	<p>South Africa. There are no patents in rest of Sun-Saharan African countries.</p>	<p>Royalty-free non-exclusive licences.</p> <p>Detailed terms and conditions are confidential.</p>

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
Elvitegravir	Gilead	<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-licencees in India currently have signed agreements with the MPP: Emcure; Aurobindo; MedChem.</p> <p>In 2011, in a separate arrangement, Gilead also signed semi-exclusive licences for the supply of COBI with four Indian manufacturers:</p> <ul style="list-style-type: none"> • Matrix: for Sri Lanka, Thailand • Hetero and Ranbaxy: for Botswana, Namibia • Strides: for Ecuador, El Salvador, Indonesia, Kazakhstan, Turkmenistan. <p>In addition to these semi-exclusive territories, these ‘preferred’ licencees can also cover territories mentioned in Gilead-MPP licences. Detailed terms and conditions of these licences are confidential.</p>	<p>100 countries: Afghanistan; Angola, Anguilla, Antigua and Barbuda, Armenia, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d’Ivoire, Cuba, Djibouti, Dominica, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Jamaica, Kenya, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Moldova, Mongolia, Mozambique, Myanmar, Nauru, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Palau, Papua New Guinea, Rwanda, St Kitts and Nevis, Saint Lucia, St Vincent and the Grenadines, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Suriname, Swaziland, Syria, Tajikistan, Tanzania, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe.</p>	<p>Non-exclusive royalty-bearing granted to the Medicines Patent Pool. Royalty of 5%; no royalties on paediatric versions developed by licencees.</p> <p>Gilead licences with MPP are only the agreements where full terms are public. There is an India specific manufacturing restriction with further limitation on territories where drugs can be supplied. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p> <p>As a part of the 2011 semi-exclusive licences with four ‘preferred’ Indian generic manufacturers, Gilead will charge 10–15% royalties.</p>
Etravirine (ETV)	Janssen (Johnson & Johnson)	<p>In 2009, Janssen (J&J) signed a licence agreement with the following company: Aspen and Emcure.</p>	Sub-Saharan Africa and least-developed countries.	Royalty-free non-exclusive licence. Aspen will register and distribute ETV formulations at a special price. Detailed terms and conditions are confidential.
Lamivudine (3TC)	GSK After Pfizer and GSK jointly announced the creation of a new joint venture on HIV medicines, all licences were transferred to ViiV.	<p>Since 2001, ViiV has signed 11 licence agreements, including with the following companies: Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos.</p>	69 countries: sub-Saharan Africa + least-developed countries + low-income countries.	<p>Non-exclusive licences.</p> <p>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.</p> <p>According to ViiV’s website, all voluntary licences are now royalty-free.</p> <p>Detailed terms and conditions are confidential.</p>
Nevirapine (NVP)	Boehringer Ingelheim (BI)	<p>Since 2004, BI 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>	78 countries: least-developed countries + low-income countries + sub-Saharan Africa.	<p>Initially, BI signed royalty-bearing licence agreements allowing for manufacturing.</p> <p>In 2007, BI changed its policy to non-assert declarations allowing distribution at no additional costs. The only condition is that licencees must be produce WHO-prequalified nevirapine products. Companies may request a royalty-free licence for manufacturing in WHO-prequalified plants.</p>

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
Raltegravir (RAL)	Merck	<p>Since 2011, Merck signed licence agreements with the following companies: Emcure; Mylan (Matrix).</p> <p>In 2010 Brazilian Ministry of Health has announced that it is working on a technology transfer agreement with Merck for RAL. The agreement has yet not been signed formally and its proposed terms and conditions are not public.</p>	60 countries: sub-Saharan Africa and low-income countries.	Non-exclusive licences. Detailed terms and conditions are confidential.
Rilpivirine	Janssen (Johnson & Johnson)	<p>Since 2011, Janssen (J&J) has signed licence agreements with the following companies: Aspen; Emcure; Hetero; Mylan (Matrix); Strides.</p>	<p>Originally 66 countries: sub-Saharan Africa + least-developed countries + India. Expanded in late 2011 to include 112 countries</p> <p>The generic pharmaceutical manufacturers in India will have rights to market the product in sub-Saharan Africa, least-developed countries and India.</p> <p>Aspen will have rights to market the product in sub-Saharan Africa including South Africa.²⁷⁶</p>	<p>Royalty-bearing voluntary non-exclusive licence.</p> <p>Licensees will manufacture, register, market and distribute rilpivirine both as a single agent and fixed-dose combination.</p> <p>Detailed terms and conditions are confidential.</p>
Saquinavir (SQV)	Roche	<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>	Sub-Saharan Africa and least-developed countries.	Detailed terms and conditions are confidential.
Stavudine (d4t)	Bristol-Myers Squibb (BMS)	<p>Since 2001, BMS signed licence agreements with the following companies: Adcock Ingram; Aspen; Danpong-Adams; Enalenj; Sonke; Varichem; Thembalani; AfrikaBiopharm; Aurobindo; Emcure; Ranbaxy.</p>	49 countries: sub-Saharan Africa + India.	<p>11 immunity-from-suit agreements allowing generic companies to produce d4t and ddl. The agreements are royalty-free, include paediatric formulations.</p> <p>The agreements also cover didanosine.</p>

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments	
Tenofovir (TDF)	Gilead	<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>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 and Emcure, who had originally signed the 2006 licences, took advantage of a key provision in the Gilead-Medicines Patent Pool licence, which permits a licensee to terminate the licence on a drug-by-drug basis, to terminate part of the 2006 licence in relation to TDF, so these companies are now free to supply TDF without paying royalty to Gilead under the 2006 licence. Aurobindo and Emcure are now sub-licensees to the Medicines Patent Pool.</p>	<p>Originally 95 countries, expanded in July 2011 to 112 countries: Afghanistan; Angola, Anguilla, Antigua and Barbuda, Armenia, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Cuba, Djibouti, Dominica, Dominican Rep., Ecuador, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Jamaica, Kazakhstan, Kenya, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Moldova, Mongolia, Montserrat, 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, Sri Lanka, Sudan, Suriname, Swaziland, Syria, Tajikistan, Tanzania, Thailand, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Turkmenistan, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe.</p> <p>The 2011 Gilead-Medicines Patent Pool licence for TDF product covers the same 112 territories.</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. The TDF patent in India was eventually rejected but 2006 licensees nevertheless continued working under the arrangements with Gilead.</p> <p>Non-exclusive royalty-bearing licences.</p> <p>Royalty rate of 5% lowered to 3% in July 2011; no royalties on paediatric versions developed by licensees.</p> <p>Gilead licences with MPP are only the agreements where full terms are public. There is an India specific manufacturing restriction with further limitation on territories where drugs can be supplied. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p>	
Zidovudine (AZT)	GSK	<p>After Pfizer and GSK jointly announced the creation of a new joint venture on HIV medicines, all licences were transferred to ViiV.</p>	<p>Since 2001, ViiV has signed 11 licence agreements, including with the following companies: Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos.</p>	<p>69 countries: sub-Saharan Africa + least-developed countries + low-income countries.</p>	<p>Non-exclusive licences.</p> <p>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.</p> <p>According to ViiV's website, all voluntary licences are now royalty-free.</p> <p>Detailed terms and conditions are confidential.</p>
3TC/AZT	GSK	<p>After Pfizer and GSK jointly announced the creation of a new joint venture on HIV medicines, all licences were transferred to ViiV.</p>	<p>Since 2001, ViiV has signed 11 licence agreements, including with the following companies: Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos.</p>	<p>69 countries: sub-Saharan Africa + least-developed countries + low-income countries.</p>	<p>Non-exclusive licences.</p> <p>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.</p> <p>According to ViiV's website, all voluntary licences are now royalty-free.</p> <p>Detailed terms and conditions are confidential.</p>

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
Rilpivirine/ TDF/3TC	Janssen (Johnson & Johnson)	<p>Since 2011, Janssen (J&J) has signed licence agreements with the following companies: Aspen; Emcure; Hetero; Mylan (Matrix); Strides.</p>	<p>Originally 66 countries: sub-Saharan Africa + least-developed countries + India. Expanded in late 2011 to include 112 countries.</p> <p>The generic pharmaceutical manufacturers in India will have rights to market the product in sub-Saharan Africa, least-developed countries and India.</p> <p>Aspen will have rights to market the product in sub-Saharan Africa including South Africa.²⁷⁶</p>	<p>Royalty-bearing voluntary non-exclusive licence.</p> <p>Licensees will manufacture, register, market and distribute rilpivirine both as a single agent and fixed-dose combination.</p> <p>Detailed terms and conditions are confidential.</p>
TDF/FTC	Gilead	<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>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 and Emcure, who had originally signed the 2006 licences, took advantage of a key provision in the Gilead-Medicines Patent Pool licence, which permits a licensee to terminate the licence on a drug-by-drug basis, to terminate part of the 2006 licence in relation to TDF, so these companies are now free to supply TDF without paying royalty to Gilead under the 2006 licence. Aurobindo and Emcure are now sub-licensees to the Medicines Patent Pool.</p>	<p>Originally 95 countries, expanded in July 2011 to 112 countries: Afghanistan, Angola, Anguilla, Antigua and Barbuda, Armenia, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, Botswana, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Cuba, Djibouti, Dominica, Dominican Rep., Ecuador, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Jamaica, Kazakhstan, Kenya, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Moldova, Mongolia, Montserrat, 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, Sri Lanka, Sudan, Suriname, Swaziland, Syria, Tajikistan, Tanzania, Thailand, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Turkmenistan, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe.</p> <p>2011 Gilead-Medicines Patent Pool licence also covers TDF product for the same 112 territories.</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>Non-exclusive royalty-bearing licences.</p> <p>Royalty rate of 5% lowered to 3% in July 2011; no royalties on paediatric versions developed by licensees.</p> <p>Gilead licences with MPP are only the agreements where full terms are public. There is an India specific manufacturing restriction with further limitation on territories where drugs can be supplied. Countries such as China, Brazil, Sri Lanka, and Indonesia are excluded.</p>

Product	Patent-holding company	Generic Company Licensees	Eligible Countries	Comments
The 'Quad' (TDF/FTC/COBI/elvitegravir)	Gilead	<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: Emcure; Aurobindo; MedChem.</p> <p>In 2011 as a separate arrangement Gilead also signed following semi-exclusive licences with four Indian manufacturers:</p> <ul style="list-style-type: none"> • Matrix: for Sri Lanka, Thailand • Hetero/Ranbaxy: for Botswana, Namibia • Strides: for Ecuador, El Salvador, Indonesia, Kazakhstan, Turkmenistan. <p>In addition to these semi-exclusive territories these licensees can also cover territories mentioned in Gilead-MPP licences. Detailed terms and conditions of these licences are confidential.</p>	<p>100 countries: Afghanistan, Angola, Anguilla, Antigua and Barbuda, Armenia, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, Botswana, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Cuba, Djibouti, Dominica, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Jamaica, Kenya, Kiribati, Kyrgyzstan, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Moldova, Mongolia, Mozambique, Myanmar, 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, Sudan, Suriname, Swaziland, Syria, Tajikistan, Tanzania, Timor-Leste, Togo, Tonga, Trinidad and Tobago, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Yemen, Zambia, Zimbabwe.</p>	<p>Non-exclusive royalty-bearing granted to the Medicines Patent Pool. Royalty of 5%; no royalties on paediatric versions developed by licensees.</p> <p>Gilead licences with MPP are only the agreements where full terms are public. There is an India specific manufacturing restriction with further limitation on territories where drugs can be supplied. Countries such as China, Brazil, Ukraine, Sri Lanka, and Indonesia are excluded.</p> <p>For Gilead 2011 semi-exclusive licences with four Indian generic manufacturers Gilead will charge 10–15% royalties.</p>

ANNEX 4: SUGGESTED RESOURCES FOR FURTHER INFORMATION

For documentation on prices reported by countries:

WHO Global Price Reporting Mechanism <http://www.who.int/3by5/amds/price/hdd/>

The Global Fund Price and Quality Reporting Mechanism <http://www.theglobalfund.org/en/procurement/pqr/>

Management Sciences for Health (MSH) International Drug Price Indicator Guide <http://erc.msh.org/mainpage.cfm?file=1.0.htm&id=1&temptitle=Introduction&module=DMP&language=English#top>

For documentation on patents:

Determining the patent status of essential medicines in developing countries, Health Economics and Drugs, EDM Series No. 17, UNAIDS/WHO/MSF, 2004. <http://apps.who.int/medicinedocs/index/assoc/s14154e/s14154e.pdf>

HIV/AIDS medicines and related supplies: Contemporary context and procurement. Technical guide. Chapter 2 and Annex B. World Bank, Washington, DC, 2004 <http://siteresources.worldbank.org/INTPROCUREMENT/Resources/Technical-Guide-HIV-AIDS.pdf>

Drug patents under the spotlight. Sharing practical knowledge about pharmaceutical patents, MSF, June 2004. <http://www.msfacecess.org/our-work/overcoming-barriers-access/article/939>

Knowledge Ecology International <http://www.keionline.org> (Archives also at <http://www.cptech.org/ip/health/>)

The Patent Status Database for Selective HIV Medicines. Medicines Patent Pool [Online]. 2011. <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>

Amin, Tahir. HIV Drug Patents in China – Full Report. [Online]. 2010 May. Available from: Initiative for Medicines, Access & Knowledge: <http://www.imak.org/storage/IMAK%20HIV%20Drug%20Patents%20in%20China%20Tahir%20Amin%20May%202010.pdf>

World Intellectual Property Organization, Patent Landscape Report on Ritonavir [Online] 2011 October. http://www.wipo.int/freepublications/en/patents/946/wipo_pub_946.pdf

For documentation on quality:

Prequalification Programme managed by the World Health Organization (WHO) <http://mednet3.who.int/prequal/>

US Food and Drug Administration (FDA) Tentative Approvals <http://www.fda.gov/cder/ogd/approvals/>

US Food and Drug Administration (FDA) Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

Other useful websites referenced in this document:

US Food and Drug Administration Orange Book <http://www.fda.gov/cder/ob/>

Catalogue of US Food and Drug Administration Approved Drug Products <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

WHO Regulatory status database <http://www.who.int/hiv/amds/patents/registration/en/index.html>

WHO Antiretroviral Therapy for HIV Infection <http://www.who.int/hiv/topics/treatment/en/index.html>

UNTANGLING THE WEB ONLINE:

Médecins Sans Frontières' guide to the prices of HIV medicines is now in its 15th edition – and is available in an online version. Please check utw.msfacecess.org

For those seeking a historical perspective, previous editions of Untangling the Web can also be found at: <http://utw.msfacecess.org>

MSF Access Campaign: <http://www.msfacecess.org>

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ANNEX 6: THE CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) PRICE LIST (AS OF MAY 2012)



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. The following information was supplied by CHAI.

SUPPLIERS & PRODUCTS

CHAI has agreements with eight manufacturers of ARV formulations, active pharmaceutical ingredients and/or pharmaceutical intermediates: Aurobindo Pharma, Cipla Ltd., Emcure Pharmaceuticals, Hetero Drugs, Micro Labs, Matrix Laboratories, Ranbaxy Laboratories and Strides Arcolabs. The ARVs included in CHAI's pricing agreements are: abacavir (ABC), atazanavir (ATV), efavirenz (EFV), emtricitabine (FTC), lamivudine (3TC), lopinavir/ritonavir (LPV/r), nevirapine (NVP), ritonavir (RTV), stavudine (d4T), tenofovir (TDF) and zidovudine (AZT).

TERMS & CONDITIONS

Prices listed below are available to countries participating in the CHAI Procurement Consortium, which currently includes over 70 nations. These prices apply to procurements by national governments that are members of the CHAI Procurement Consortium, or organizations procuring on behalf of member governments, to support public care and treatment programs. Products should be purchased directly from partner suppliers or through procurement agents representing the aforementioned programs. For TDF products offered by suppliers under a voluntary licence from Gilead, indicated pricing is available only to countries covered under the voluntary licence. Please contact 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 below are FCA Airport from the point of export. Annual treatment costs for pediatric formulations are determined based on the recommended daily dosing for a 10kg child (unless a formulation is not recommended for a 10kg child, in which case the annual price is calculated based on dosing for an applicable weight band).

QUALITY

CHAI is committed to the sustainable supply of high-quality ARVs, consistent with the specifications of dossiers approved by the World Health Organization (WHO), U.S. Food and Drug Administration (U.S. FDA), or a stringent regulatory authority (SRA) as defined by the International Conference on Harmonization (ICH). In the list below, footnotes specify the applicable quality assurance status for each formulation: (1) Approved by the WHO Prequalification Programme; (2) Approved by the U.S. FDA or other SRA; (3) Submitted to the WHO, U.S. FDA or other SRA for review and recommended for procurement by Expert Review Panel (ERP) of The Global Fund; (4) Submitted to the WHO, U.S. FDA or other SRA for review but not yet recommended by ERP.

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

ADULT PRODUCTS		2012 CEILING PRICE (USD)			SUPPLIER							
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Emcure	Hetero	MacLeods	Matrix	Ranbaxy	Micro
3TC (150mg)	HDPE bottle 60 tablets	\$31	\$2.6	\$0.04	✓ ²	✓ ¹		✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹	✓ ³
ABC (300mg)	HDPE bottle 60 tablets	\$186	\$15.5	\$0.26	✓ ²					✓ ^{1,2}		
AZT (300mg)	HDPE bottle 60 tablets	\$89	\$7.4	\$0.12	✓ ²	✓ ^{1,2}		✓ ^{1,2}		✓ ^{1,2}	✓ ¹	✓ ¹
AZT (300mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$105	\$8.8	\$0.15	✓ ²	✓ ^{1,2}	✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹	✓ ¹
AZT (300mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$134	\$11.2	\$0.19	✓ ²	✓ ^{1,2}		✓ ^{1,2}		✓ ^{1,2}	✓ ¹	
ATV (300mg)	HDPE bottle 30 capsules	\$265	\$22.1	\$0.74			✓ ²			✓ ^{1,2}		
d4T (30mg)	HDPE bottle 60 capsules	\$24	\$2.0	\$0.03	✓ ²				✓ ¹		✓ ¹	
d4T (30mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$45	\$3.8	\$0.06		✓ ^{1,2}		✓ ²	✓ ²		✓ ¹	
d4T (30mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$79	\$6.6	\$0.11		✓ ^{1,2}	✓ ²	✓ ^{1,2}	✓ ²		✓ ¹	
EFV (600mg)	HDPE bottle 30 tablets	\$55	\$4.6	\$0.15	✓ ²		✓ ²			✓ ^{1,2}	✓ ¹	
LPV/r (200/50mg)	HDPE bottle 120 tablets	\$378	\$31.5	\$0.26	✓ ²					✓ ^{1,2}		
NVP (200mg)	HDPE bottle 60 tablets	\$36	\$3.0	\$0.05	✓ ²		✓ ²	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ¹	
RTV (100mg) heat stable*	HDPE bottle 30 tablets	\$90	\$7.5	\$0.25						✓ ^{1,2}		
TDF (300mg)	HDPE bottle 30 tablets	\$58	\$4.8	\$0.16	✓ ²			✓ ²		✓ ^{1,2}	✓ ¹	
TDF + 3TC (300/300mg)*	HDPE bottle 30 tablets	\$70	\$5.8	\$0.19	✓ ²			✓ ^{1,2}		✓ ^{1,2}		
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	\$97	\$8.1	\$0.27	✓ ²			✓ ²		✓ ^{1,2}		
TDF + 3TC + EFV (300/300/600mg)	HDPE bottle 30 tablets	\$159	\$13.3	\$0.44						✓ ^{1,2}		
TDF + FTC + EFV (300/200/600mg)	HDPE bottle 30 tablets	\$183	\$15.3	\$0.51						✓ ^{1,2}		
ATV (300mg)/RTV (100mg)	HDPE bottle 30 tablets	\$276	\$23.0	\$0.77						✓ ^{1,2}		
ATV (300mg)/RTV (100mg) + TDF/3TC (300/300mg)	2 HDPE bottle 30 tablets each of ATV/RTV + TDF/3TC	\$346	\$28.8	\$0.96						✓ ^{1,2}		

*Abbott, the originator for the heat-stable formulation of RTV, has an access pricing policy of its own and has not joined CHAI's ceiling price agreement. The company supplies the drug at a reduced price of \$42 per person per year to its Category 1 countries, which includes countries in sub-Saharan Africa and all other Least-Developed Countries. Thus, when the individual components are purchased separately from different suppliers, the TDF+3TC+ATV+RTV regimen is available at less than \$410 per person per year.

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

PAEDIATRIC PRODUCT		2012 CEILING PRICE (USD)			SUPPLIER			
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Matrix	Strides
3TC (50mg/5ml)	HDPE bottle 240ml	\$28	\$1.85	\$0.01	✓ ²			
ABC (20mg/ml)	HDPE bottle 240ml	\$203	\$13.50	\$0.06	✓ ²	✓ ^{1,2}		
ABC 60mg	HDPE bottle 60 tablets	\$125	\$5.20	\$0.09	✓ ²		✓ ^{1,2}	
ABC (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$132	\$5.50	\$0.09	✓ ²		✓ ^{1,2}	
AZT (50mg/5ml)	HDPE bottle 240ml	\$63	\$2.10	\$0.01	✓ ²			
AZT (100mg)	HDPE bottle 100 capsules	\$34	\$4.75	\$0.05	✓ ²			
AZT (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$74	\$3.10	\$0.05	✓ ²	✓ ^{1,2}	✓ ^{1,2}	
AZT (60mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$102	\$4.25	\$0.07			✓ ^{1,2}	
d4T (1mg/ml)	HDPE bottle 200ml	\$50	\$1.40	\$0.01	✓ ²			
d4T (15mg)	HDPE bottle 60 capsules	\$17	\$1.40	\$0.02	✓ ²			
d4T (20mg)	HDPE bottle 60 capsules	\$9	\$1.45	\$0.02	✓ ²			
d4T (6mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$46	\$1.90	\$0.03		✓ ^{1,2}		
d4T (12mg) + 3TC (60mg)	HDPE bottle 60 tablets	\$40	\$3.30	\$0.06		✓ ^{1,2}		
d4T (6mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$55	\$2.30	\$0.04		✓ ^{1,2}		
d4T (12mg) + 3TC (60mg) + NVP (100mg)	HDPE bottle 60 tablets	\$52	\$4.30	\$0.07		✓ ^{1,2}		
EFV (50mg)	HDPE bottle 30 tablets	\$27	\$2.40	\$0.08	✓ ²		✓ ²	
EFV (200mg)	HDPE bottle 90 scored tablets	\$38	\$9.60	\$0.11				✓ ^{1,2}
LPV/r (100/25mg)	HDPE bottle 120 tablets	\$204	\$17.00	\$0.14	✓ ²		✓ ^{1,2}	
LPV/r (80 + 20mg/ml)*	HDPE bottle 300ml	\$289	\$57.75	\$0.19		✓ ³		
NVP (50mg/5ml)	HDPE bottle 240ml	\$57	\$1.90	\$0.01		✓ ¹		

*Price includes a measuring device such as a syringe, which was not included in the prior ceiling price list.



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GLOSSARY AND ABBREVIATIONS

3TC: Lamivudine; nucleoside analogue reverse transcriptase inhibitor.

ABC: Abacavir; nucleoside analogue reverse transcriptase inhibitor.

AIDS: Acquired Immune Deficiency Syndrome.

API: Active pharmaceutical ingredient.

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

ARV: Antiretroviral medicine to treat HIV/AIDS.

ATV: Atazanavir, protease inhibitor.

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

BI: Boehringer Ingelheim.

BMS: Bristol-Myers Squibb.

Category 1: In this document, 'Category 1' is used to describe those countries that are eligible for the most discounted price offered by a company.

Category 2: In this document, 'Category 2' is used to describe those countries that are not eligible for the lowest prices reserved for category 1 countries, but are nevertheless offered a discount by companies.

CCRS: Chemokine coreceptor 5.

CHAI: Clinton Health Access Initiative. Since 2002, the Clinton Health Access Initiative has assisted countries in implementing large-scale, integrated care, treatment and prevention programmes.

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.

CL: Compulsory licence.

d4T: Stavudine; nucleoside analogue reverse transcriptase inhibitor.

ddl: Didanosine; nucleoside analogue reverse transcriptase inhibitor.

DRV: Darunavir, protease inhibitor.

EC: Enteric-coated.

EFV or EFZ: 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.

The 17th Model List of Essential Medicines was published in March 2011 and includes 14 antiretrovirals and five fixed-dose combinations.

EU: European Union.

EXW: 'Ex-works'. 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.

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.

FPV: Fosamprenavir; protease inhibitor.

FTC: Emtricitabine; nucleoside analogue reverse transcriptase inhibitor.

Generic Drug: According to WHO, a pharmaceutical product usually intended to be interchangeable with the originator product, which is usually manufactured without a licence from the originator company.

GPRM: WHO Global Price Reporting Mechanism. A database containing prices paid by UNICEF, the International Dispensary Association (IDA), Management Sciences for Health (MSH)/Deliver, and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

GSK: GlaxoSmithKline.

HDI: Human Development Index. A summary composite index, compiled by UNDP, that measures a country's

average achievements in three basic aspects of human development: longevity (or life expectancy at birth), knowledge (or adult literacy rate and enrolment in education), and a decent standard of living (gross domestic product per capita).

HIV: Human Immunodeficiency Virus.

IDV: Indinavir; protease inhibitor.

IRBM: Institute for Research in Molecular Biology.

LDCs: Least-Developed Countries, according to United Nations classification.

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

MSD: Merck Sharp & Dome (Merck & Co., Inc.).

MSF: Médecins Sans Frontières, Doctors Without Borders.

NDRA: National Drug Regulatory Authority.

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

PEPFAR: President's Emergency Plan for AIDS Relief, a United States programme to fight HIV/AIDS in developing countries.

PI: Protease Inhibitor.

PLWHA: People Living With HIV/AIDS.

PMTCT: Prevention of Mother-to-Child Transmission.

PPLY: Per patient per year.

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.

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.

TB: Tuberculosis.

TDF: Tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

TRIPS: Trade-related Aspects of Intellectual Property Rights.

UN: United Nations.

UNAIDS: United Nations Joint Cosponsored Programme on HIV/AIDS. Created in 1996, to lead, strengthen and support an expanded response to the HIV/AIDS epidemic. The six original cosponsors are UNICEF, UNDP, UNFPA, UNESCO, WHO and the World Bank. UNDCP joined in April 1999.

UNDP: United Nations Development Programme.

UNITAID: Is an international drug purchase facility that was established in 2006 by Brazil, Chile, France, Norway and the United Kingdom and now includes 27 countries to provide new sources of funding to fight HIV/AIDS, malaria and tuberculosis.

US FDA: United States Food and Drug Administration.

VL: Voluntary licence.

WHO: World Health Organization.

WHO GPRM: WHO Global Price Reporting Mechanism.

WTO: World Trade Organization.

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

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