



UNTANGLING THE WEB OF
**ANTIRETROVIRAL
PRICE REDUCTIONS**

13th Edition July 2010



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Médecins Sans Frontières' guide to the prices of AIDS medicines is now in its 13th edition – and is also available in an online version. Stay up-to-date with the latest news on ARV prices and availability by checking:

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THE MSF CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

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



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NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI & NtRTI)

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29	Didanosine (ddl)
31	Emtricitabine (FTC)
32	Lamivudine (3TC)
34	Stavudine (d4T)
36	Tenofovir disoproxil fumarate (TDF)
38	Zidovudine (AZT or ZDV)

PROTEASE INHIBITORS (PI)

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44	Fosamprenavir (FPV or f-APV)
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BACKGROUND: ACCESS TO ANTIRETROVIRALS

AIDS PROGRESS UNDER SIEGE: THE EMERGENCY IS FAR FROM OVER

HIV/AIDS is a lifelong disease, and although there is no cure, treatment with antiretroviral drugs (ARVs) prolongs and improves the quality of life.

AIDS treatment in developing countries began roughly a decade ago, mostly as small pilot projects and in the face of widespread scepticism about its feasibility in resource-poor settings. MSF was one of the first organisations to provide antiretroviral therapy (ART) in developing countries, starting with projects in Thailand and South Africa in 2000.^{1,2}

MSF is currently supporting care and treatment for more than 154,000 people in 27 countries. By the end of 2008, a total of four million people across the developing world were on ART.¹

Delivering ART to millions of people in developing countries was made possible because treatment was brought close to where people lived, the price of medicines came down dramatically, and treatment was simplified and made more patient-friendly, with several medicines combined into one pill (known as a fixed-dose combination, or FDC). And in order to address the shortages of medical staff in many countries, tasks are being shifted, so that nurses or nurse aides can perform many of the duties previously reserved for doctors.

While these achievements represent important progress, the crisis is far from over. Until recently it was estimated that almost 10 million people are in immediate need of treatment, a testament to the persistent emergency.² With the revision of the World Health Organization (WHO) guidelines in late 2009⁹, which recommend, in line with current evidence, that treatment be initiated earlier in a patient's disease progression, the number of patients in need of ART is expected by some to increase by a further five million to

around 14 million people.³ The number of people who will need treatment by 2030 has been projected to reach as many as 55 million.⁴

At the same time, with growing numbers of patients in developing countries having been on treatment for five years or longer, new challenges are emerging to ensure their long-term survival. For treatment to be most successful, patients need to be monitored effectively and have access to newer and more potent drugs when they inevitably develop resistance or side effects to their medicines over time. But most newer drugs are unaffordable because of high monopolistic prices and crucial monitoring tests are not adapted for use in resource-poor settings.

However, the international AIDS effort is at a critical juncture, compromised

further by the response of world leaders to the economic crisis: the two main funding sources for HIV/AIDS in developing countries, the Global Fund to Fight AIDS, Tuberculosis and Malaria and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), will not be able to support the treatment scale-up at its current rate given insufficient donor commitment. The Global Fund is facing a significant financing gap and PEPFAR's funding levels are flat.¹⁸⁷ Barely four years after world leaders met at the 2006 United Nations General Assembly and committed to universal access to HIV prevention, treatment and care, political and funding support is waning.

Extending ARV treatment in developing countries to all people in need, while ensuring patients can survive with HIV in the long-term, will require much more investment and political will.

'We're at a fork in the road: either governments summon the political will and financial resources to treat AIDS in developing countries, or current funding for AIDS treatment stagnates, which means patients will see their treatment delayed, deferred and denied. It's a question of choice: if they don't help us treat AIDS, there will be more graves.'

***Dr. Tido von Schoen-Angerer,
Director of MSF's Campaign for Access to Essential Medicines***



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'The number of people needing HIV treatment will rise over the next two decades and so will the cost of treatment. This is because better, more effective treatments have come on the market and should be offered to patients, and also because, over time, more people will move from first- to-second (and later) line regimens, which are more expensive.'

The Treatment Timebomb – Report of the Enquiry of the UK All Party Parliamentary Group on AIDS⁴

CHALLENGES: SECOND-CLASS AIDS TREATMENT

There is a growing disconnect between the AIDS treatment available to people in developed countries and to their counterparts in developing countries. In wealthy countries, AIDS now resembles a chronic disease, much like heart disease or diabetes, and patients generally have access to an increasing variety of treatment options once they inevitably develop drug resistance.⁵

In contrast, people living with HIV/AIDS in developing countries largely have access to only one combination of medicines that causes significant side effects, with few or no alternatives for when their treatment fails. And the youngest people living with AIDS continue to be an afterthought – paediatric treatment still lags behind that for adults, as does the development of appropriate ARVs for children.

If people living with HIV/AIDS are to be given the same prospects for survival whether they live in developing countries or in wealthy countries, urgent action must be undertaken to ensure access:

- to a less toxic first-line regimen;
- to second- and third-line treatment options, as patients develop resistance;

- to better and timely detection of treatment failure, through viral load testing; and
- to paediatric AIDS treatment options, which must be prioritised, together with the prevention of mother-to-child transmission of the virus.

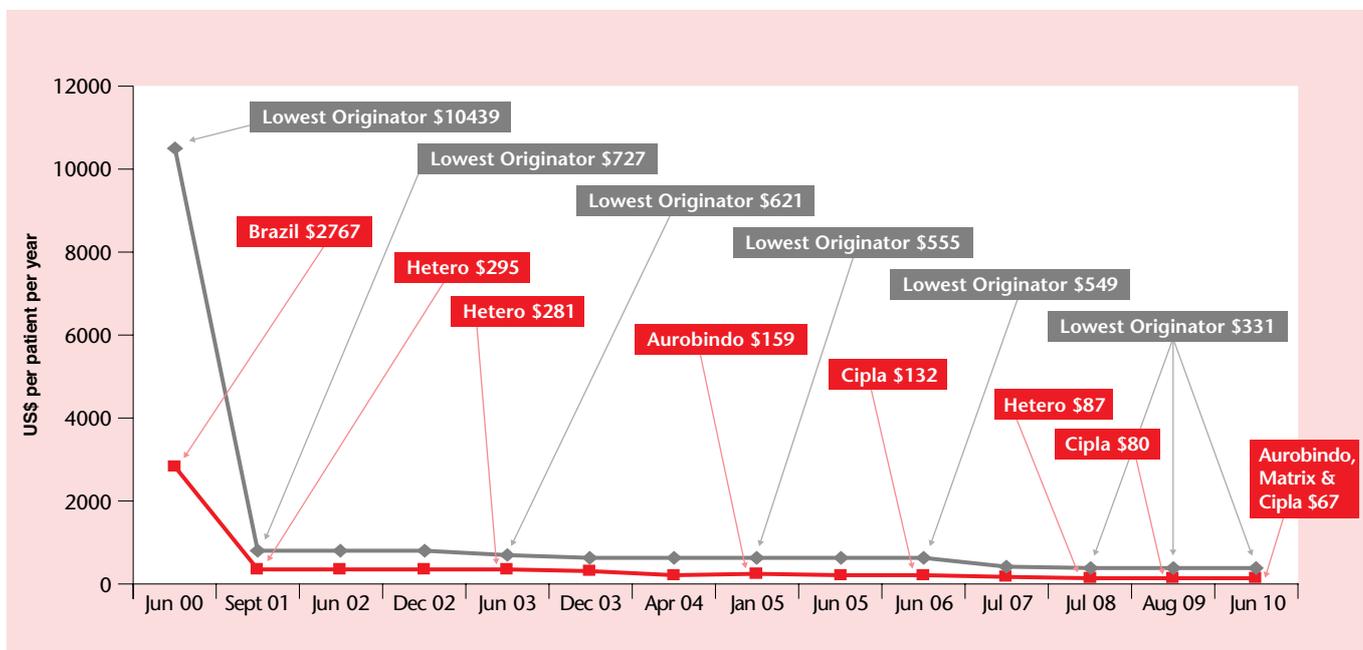
A) Move to a less toxic and more robust first-line regimen

The first line of defence to help slow the pace at which patients need to switch to newer, more expensive ARV treatment regimens is a robust first-line drug combination with few side effects.

Today, the majority of people on their first-line of ARVs in low- and middle-income countries receive the combination of lamivudine/stavudine/

nevirapine (3TC/d4T/NVP).⁶ Thanks to generic competition, this regimen now costs US\$ 67 per patient per year (ppy) – 99% less than 10 years ago. This dramatic price drop was possible because of competition among multiple generic manufacturers in countries where these drugs were not patented, such as Brazil, Thailand and India (see graph 1).

Notwithstanding the dramatic price drop over the past decade, using this standard combination comes at a high medical cost. The drug stavudine (d4T) causes serious side effects, some intolerable, such as peripheral neuropathy. It can also lead to lactic acidosis, which in rare cases can lead to death. It also causes stigmatisation because over long-term treatment, patients develop easily recognisable facial wasting.



GRAPH 1: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTIONS.

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

Stavudine is virtually no longer used in wealthy countries (in 2006, for example, fewer than 2% of patients in Switzerland were taking the drug⁷). Patients in these countries are offered better-tolerated alternatives, such as tenofovir (TDF) or zidovudine (AZT). Since 2006, WHO has recommended in its HIV/AIDS treatment guidelines that treatment providers begin moving away from stavudine-based regimens because of their long-term irreversible side effects, towards tenofovir or zidovudine-containing regimens.⁸

This call was repeated in the latest recommendations released by WHO in December 2009 for ART for HIV in adults and adolescents, advising countries to develop a plan to move towards tenofovir or zidovudine-based first-line regimens.⁹

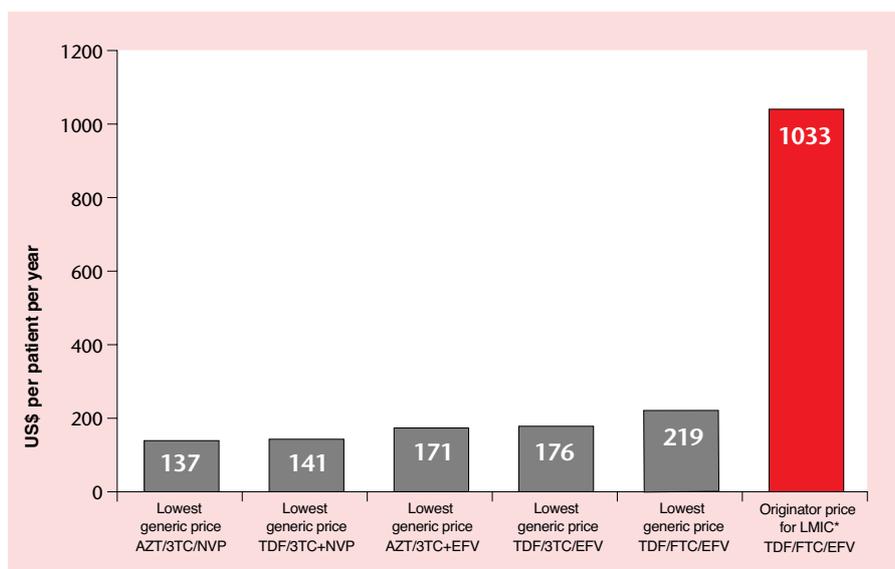
But until now, the significantly higher costs of these alternatives have largely prevented this switch in many developing countries. Better, less-toxic first-line regimens are still at best nearly double the price of the stavudine-based first-line regimen.

However, there has been a noteworthy downward trend in the prices of less-toxic first-line combinations. The price of tenofovir has come down significantly over the past few years, by almost 77%. This means that TDF-based combinations are now nearly the same price as those containing zidovudine (see graph 2). Fixed-dose combinations containing zidovudine (AZT/3TC/NVP) and those

containing tenofovir (TDF/3TC/EFV) have both fallen, by 17% and 59% respectively in the past three years.

It is thanks to generic competition that these prices are steadily coming down, and they can be expected to fall further as demand increases. In countries where the drugs are not under patent or where patent owners permit such competition, the one-pill-once-a-day generic triple combination containing

tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is now available for \$176 ppy (see graph 2). But in some lower middle-income countries, patent owners do not permit access to generic products, meaning that countries have to rely on the 'discounted' price offered by originator companies. For tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV), this means a price almost six times more expensive, at \$1,033 ppy.



*LMIC – Lower middle-income countries (see annex 6)

GRAPH 2: THE PRICE OF NEWER, IMPROVED FIRST-LINE REGIMENS IN 2010.

Generic competition has allowed newer, improved first-line regimens recommended by WHO to fall in price, but in some countries, patent protection means prices stay at unaffordable levels.

The price of treatment is clearly a critical concern. But the long-term benefits of patients being able to tolerate and stay on their first ARV combination longer can outweigh the costs. A study in Lesotho showed that using a generic

tenofovir-based regimen results in better quality of life for patients as compared to a stavudine-based regimen.¹⁰ And while shifting treatment programmes to a new first-line regimen brings with it clear logistical challenges on top of

cost concerns, it is critical that treatment providers begin moving away from stavudine as has been done for example in Zambia, Lesotho, Guyana, South Africa and Botswana.

DESIGN HIV DRUGS WITH DEVELOPING COUNTRY NEEDS IN MIND

With 95% of people with HIV/AIDS living in developing countries, it is urgent that research and development take into account the particular needs of these populations. Such considerations must be systematically integrated into the early stages of the drug development process.

Over the last three years, there have been significant advances in HIV medicine, which have led to a number of new drugs from older classes, as well as entirely new therapeutic classes being approved for use. The new drug classes have different mechanisms of action to target the HIV virus, providing people living with HIV/AIDS with additional treatment options.

However, since ARVs are developed primarily for developed country markets, data relevant to address the specific needs of populations in developing countries, such as pregnant women or people who also need to take drugs for tuberculosis due to co-infection, is not obtained in clinical trials. A further example is the lack of knowledge about the interactions between antimalarials and antiretrovirals,¹² even though 80% of people living with HIV live in regions where malaria is endemic.¹³

Further, there is currently no safety and efficacy data for children for the new drugs etravirine, maraviroc, or raltegravir. For other drugs there are limited data: for efavirenz (no data for children under three years),

atazanavir and darunavir (no data for children under six years). This despite the fact that the U.S. Food and Drug Administration (FDA) has included incentives and obligations to encourage submission of data for paediatric use since 1997¹⁴ and the European Medicines Agency (EMA) followed suit in January 2007.¹⁵

The need for high-tech monitoring can also affect the availability of antiretrovirals. For instance, the entry inhibitor maraviroc requires a complicated diagnostic test costing more than US\$ 1,900 – a factor making its use impracticable and unaffordable in developing country contexts where even simple laboratory monitoring is rarely available.



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B) SECURE ACCESS TO SECOND- AND THIRD-LINE REGIMENS

Lifelong AIDS treatment requires constant access to newer and more potent drug regimens when patients develop side effects or resistance to their medicines over time. Although resistance is an inevitable element of long-term treatment, it can be delayed by using drug combinations with fewer side effects to facilitate adherence, and can be limited by changing treatment soon after viral suppression begins to wane. New WHO guidelines on second-line further simplify and prioritise the choice of regimens.

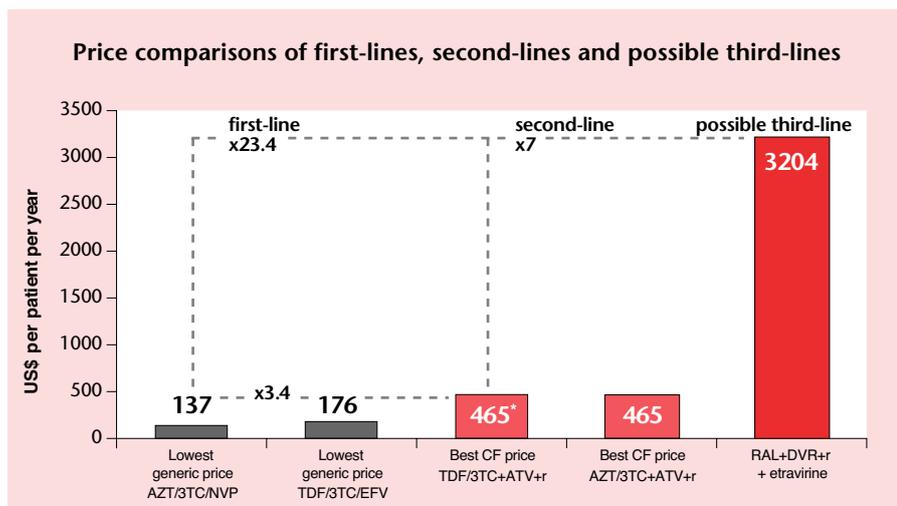
Demand for newer AIDS drugs is growing fast. In one of MSF's longest-running AIDS treatment programmes, in Khayelitsha, South Africa, 14% of patients on treatment for five years needed to switch to a second-line drug combination because of virological failure.²⁴ And 25% of those patients who switched again developed virological failure to their second-line regimen a further two years later.¹⁸⁸

MSF's Khayelitsha data provides a window into the growing need for access to newer AIDS drug regimens across the developing world in the coming years. As some patients in developing countries have already developed resistance to their second-line regimen, it is crucial to secure further treatment options essential to long-term survival. However, the price of newer regimens remains a major barrier to access.

GRAPH 3: THE TREATMENT TIME BOMB: THE IMPACT OF SWITCHING TO SECOND- AND THIRD-LINE REGIMENS ON THE PRICE OF ARV TREATMENT.

Changing a patient's regimen because of side effects or the emergence of resistance means relying on newer, patented, and therefore more expensive drugs. The price of a possible third-line regimen may cost at least 23 times more than the most affordable first-line regimen, and close to seven 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.

The most affordable second-line regimen recommended by new WHO guidelines is today priced at \$465 (see graph 3). This is more than three times the most affordable of the improved first-line regimens recommended by WHO.



'Seeing a patient that you have been treating since 2003, now failing on her second combination, you feel, as a nurse, you are a failure. We are feeling like our hands are tied.'

Mpumi Mantangana, MSF nurse in Khayelitsha, South Africa

*At the time of going to press, there is no TDF/3TC + ATV+r co-pack. The Clinton Foundation-negotiated price of the individual components of this package comes to \$465. CF expects the co-pack to be available by the end of 2010. At that stage its price is expected to drop to \$425.

DEATH AT THE DOORSTEP: THEMBSISA'S STORY

'I'm so worried now because I don't know what is going to happen to me,' says Thembsisa Mkhosana, a mother of two who lives in Khayelitsha, South Africa. Thembsisa discovered she was HIV-positive in 2001 and began receiving ART through MSF's clinic two years later. She responded well to treatment and was able to return to work and take care of her children.

But after showing signs of treatment failure because of drug resistance,

Thembsisa was switched to a second set of ARVs. Again she developed resistance. Thembsisa now needs a third set of ARVs to keep her alive but those newer drugs are unaffordable. *'If there's no such thing that can help me, I know that I'm going to die,'* says Thembsisa. *'And then who is going to look after my children?'*

Thembsisa is but one of many patients who now need access to newer and more potent, but unaffordable ARV regimens.



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'What we are seeing in Khayelitsha is what we will soon see throughout Africa if there is not a focused push for urgent change,' says Dr. Eric Goemaere, Medical Coordinator for MSF in South Africa.

In December 2009, WHO released new recommendations which for the first time raises the need for treatment options after failure of second-line therapy. Many studies are ongoing, and the drugs likely to have anti-HIV activity in third-line regimens are darunavir (boosted with ritonavir), etravirine and raltegravir.⁹

Because of patent barriers, generic competition on these medicines is severely hampered. Unlike with the first generation of AIDS drugs, patents in key producing countries such as India prevent the production of much more affordable generic versions: many of the newer ARVs will likely be under patent in India, and several such as raltegravir,

maraviroc or etravirine already are. The lack of competition among generic manufacturers means that prices cannot be expected to come down the way they did for the first generation of ARVs.

There is no generic version of etravirine, for example. Its manufacturer, Tibotec, has just announced a 'discounted' price for Sub-Saharan Africa and least-developed countries, at \$913 ppy. A potential third-line regimen could thus be available for developing countries at the prohibitive price of \$3,204 ppy (at best, as this price applies to only Africa and least-developed countries).

There is no room for complacency about these prices. For most people who are

failing on their second-line combination already, this unaffordable price will mean they almost certainly once again face death.

It is imperative that governments undertake measures to ensure that people in need of newer and more potent ARVs are not denied access because of patent barriers. This includes, but is not limited to, the routine use of compulsory licensing and other public health safeguards set out in the TRIPS Agreement (Trade-Related Aspects of Intellectual Property Rights). The planned Medicines Patent Pool for antiretrovirals is an important additional mechanism to ensure future availability of affordable essential medicines (see box).

C) PUT AN END TO THE NEGLECT OF CHILDREN LIVING WITH HIV/AIDS

While there has been important progress in scaling-up paediatric AIDS treatment over the past year, children continue to be an afterthought when it comes to treatment and developing appropriate and adapted medicines to meet their needs. Furthermore, much more effort needs to be placed on prevention of mother-to-child transmission (PMTCT) of the virus in order to eliminate these entirely avoidable infections in the first place.

The vast majority of children with HIV/AIDS are infected through transmission from the mother during pregnancy, childbirth or breastfeeding. PMTCT has been so successful in wealthy countries that nearly no children are newly infected with AIDS. But in developing countries, nearly 430,000 new child infections occurred in 2008 – a testament to the failure to effectively implement simplified and efficient PMTCT strategies that could dramatically reduce the number of child infections.¹⁶ In the latest WHO guideline on PMTCT and infant feeding, more options have been recommended including the provision of triple ART to all HIV-positive pregnant women and introducing ways to protect the child throughout the breastfeeding period.⁷⁶ This would lessen the need for paediatric treatment, as has been seen in wealthy countries.

Because there are so few children with HIV/AIDS in wealthy countries, there is very limited investment by the pharmaceutical industry into developing appropriate and adapted paediatric ARVs.

It is noteworthy that the available paediatric FDC tablets that come in doses for various child sizes are produced mainly by generic companies.

The price of the paediatric FDC d4T/3TC/NVP, at \$53 ppy, is finally lower

than that for adults. But the fact that the first WHO prequalified paediatric ARV FDC became available only in 2006, while the adult equivalent has been available since 2001, reflects the way in which children with AIDS lag behind.

DEVELOP SIMPLE DIAGNOSTIC AND MONITORING TOOLS FOR ADULTS AND CHILDREN

It is vitally important to be able to detect when a patient is no longer responding to ART. Switching someone to a newer drug combination too late or too soon can compromise the treatment's effectiveness.

A technology used to detect the level of the AIDS virus in patients' blood – called 'viral load' testing – is the gold standard. However, it requires access to laboratories with sophisticated equipment, trained staff and the transport of blood samples, all of which can be complicated or even impossible in remote settings of poor countries.

There is an urgent need for simple and easy-to-use monitoring tests that can be used on the spot, overcoming these practical barriers. Without access to such tests, many patients are being switched too early or too late, only when they appear to be getting sick again once the virus has taken hold anew.

Furthermore, HIV/AIDS diagnosis in infants is extremely difficult. In babies under 18 months it can only be conducted with the use of a complex DNA-based diagnostic test that is expensive to conduct, also requiring trained personnel and access to sophisticated laboratory equipment. Only 15% of children born to mothers living with HIV in low- and middle-income countries were tested for HIV within the first two months of life.⁶ There is a desperate need to develop a simple diagnostic test that can be used to detect the virus in younger infants on the spot, so that treatment can be initiated as early as necessary. Early infant diagnosis is key because without treatment, half the children will die before the age of two.

Until new tools exist, however, it is urgent for donors and treatment providers to ensure that the existing diagnostic technologies are implemented as widely as possible.

Furthermore, of the 22 ARVs approved by the U.S. FDA for adults, five are not approved for use in children and six do not come in any paediatric formulations.¹⁸ When paediatric formulations do exist, the majority of them continue to be ill-adapted for use in resource-poor settings. This means they either come in powder or syrup form, with some having a bitter taste, or needing to be mixed with clean water or requiring refrigeration, both of which can be difficult to come by in many developing country contexts.

In April 2008, WHO revised its paediatric ARV treatment guidelines, recommending the use of the protease inhibitor lopinavir/ritonavir (LPV/r) for infants that have been exposed to nevirapine (NVP) directly or through their mothers.¹³⁰ This recommendation, however justified, means taking a regimen including an LPV/r syrup, which



is nearly 60% more expensive than a liquid nevirapine-based regimen and also requires refrigeration.

At the same time, there is no alternative regimen once the child fails this regimen.

There is thus an urgent need for the development of child-friendly doses of heat-stable protease inhibitors for the youngest patients. Paediatric dosing studies for the newer, more potent drugs must urgently be conducted.

OVERCOMING CHALLENGES: STAVING OFF THE SECOND WAVE OF THE ACCESS CRISIS

UNAFFORDABLE, AGAIN...

Fierce competition among multiple generic pharmaceutical manufacturers in countries such as India and Brazil, where medicines were not patented, is what brought the cost of AIDS treatment down by 99% over the past decade, from \$10,000 to \$67 ppy today. India has thus been called the 'pharmacy of the developing world,' and, for example, MSF sources more than 80% of the ARVs used in its projects from India.

A lack of patents in India additionally fostered the production of FDC pills – crucial to the simplification of treatment that has fostered global scale-up – because patents on the individual compounds did not stand in the way of combining the drugs.

But across the globe, increased product patenting in developing countries is now threatening the production of affordable

generic versions of newer medicines and the development of better FDCs. International trade rules now require the patenting of medicines in key producing countries like India and Brazil, essentially eliminating the kind of generic competition for the future that brought prices down in the past.

Under the World Trade Organization's TRIPS Agreement and the 2001 Doha Declaration on TRIPS and Public Health, LDCs are not required to grant or enforce patents on pharmaceuticals until 2016. This period therefore expires in barely six years, after which these countries will be facing patent barriers. Consideration needs to be given to have this period extended.

Tomorrow's battle for access to affordable ARVs will need to be fought in a different way. To ensure that funds stretch as far as possible to meet the

'Reducing the costs of drugs could enable savings that could fund access to life-saving treatment for an additional one million people every year, even without new resources.'

The Treatment Timebomb – Report of the Enquiry of the UK All Party Parliamentary Group on AIDS⁴

needs, policy actions are needed to contain the cost of drugs, while ensuring quality treatment for the long term.

It will require routine use of public health safeguards in patent laws and of flexibilities in the TRIPS Agreement, and the participation of pharmaceutical companies – originator and generic – in new mechanisms to boost access.

Ensuring newer medicines are made affordable for people in developing countries thus depends on:

- a country's right to design flexible patent laws that are favourable to access to medicines;
- a country's right, when essential medicines are patented and unaffordable, to issue compulsory licenses to ensure access; and
- pharmaceutical companies participating in the new Medicines Patent Pool, the innovative mechanism recently established by UNITAID.



A) DESIGN FLEXIBLE PATENT LAWS

The Doha Declaration stresses that countries have the right to design patent laws that serve the interest of public health.

When India amended its patent law in 2005, it included several key safeguards including a prohibition on the patenting of insignificant or minor improvements of known medicines. This part of the India Patents Act is known as Section 3(d). It means that pharmaceutical companies should not be able to obtain patents in India for medicines that are not actual inventions, such as combinations or slightly modified formulations of existing medicines. Such patent applications are designed to delay generic competition that could lead to lower prices.

For the first time, a country thus emphasised stricter patentability criteria for pharmaceuticals and included provisions in its patent law stipulating that patents should only be granted on medicines that are truly new and innovative.

The law also allows any interested party to oppose a patent before or after it is granted ('pre-grant' and 'post-grant' oppositions). Such oppositions have been filed in India by civil society, patient groups and generic companies from India and Brazil, with the positive outcomes that several patents on key ARVs were rejected by the Indian patent offices on the grounds that they lack an inventive step and fail to satisfy the requirements of Section 3(d) of the patent law.

PUT A STOP TO FRIVOLOUS PATENTING

The Indian Patents Act, if rigorously interpreted, provides under Section 3(d) several grounds for rejecting a patent application, for instance if the patent claimed is only a new form of a known pharmaceutical substance.

In 2006, the Indian patent office rejected Novartis' patent application for its anti-cancer drug imatinib mesylate (brand name Gleevec), on the grounds that the application claims a 'new form of a known substance' (Novartis' patent application was related to a particular crystal form of the salt of imatinib mesylate).

In essence, the Indian patent office was applying the law, as applications that do not claim real 'inventions' do not deserve a patent. Like Novartis in this example, many patent applications filed by pharmaceutical companies are for a new use of an old drug, or simply for derivatives of old drugs or combinations of old drugs.

Novartis launched legal proceedings challenging the constitutionality of Section 3(d) of India's Patents Act. This prompted MSF to launch the 'Drop the Case' petition in order to protect the 'pharmacy of the developing world'.¹⁹ Novartis lost this case in August 2007 when the Madras High Court upheld the public health safeguard.

But Novartis is not giving up. Having lost the battle to strike down Section 3(d) of India's Patents Act almost three years ago, Novartis has launched fresh legal proceedings in India to weaken this critical public health safeguard. The Swiss multinational pharmaceutical company has filed a case before the Indian Supreme Court in what can be considered the second part of the Novartis case.

This case will determine the manner in which Section 3(d) will be implemented in India.

While Section 3(d) should help safeguard against the granting of frivolous patents, there is still great concern about newer drugs, invented after 1995, which can be patented under Indian law; several such as etravirine, maraviroc, raltegravir already are.

Generic production of these newer ARVs will thus only start through licensing – be it voluntary or compulsory.

THREE DOWN; MANY MORE TO GO: OPPOSING PATENTS IN INDIA IN THE NAME OF ACCESS TO AFFORDABLE MEDICINES

Since early 2006, the Indian Network of People Living with HIV/AIDS, the Delhi Network of Positive People and the Positive Women's Network, together with other civil society groups in India and beyond have filed pre-grant oppositions against the granting of patents on ARVs recommended by WHO for first- and second-line treatment. Many of these oppositions have been filed on the basis of the patent law's Section 3(d), which prevents 'evergreening' of known medicines.

In 2006, GlaxoSmithKline withdrew its patent application for the lamivudine/zidovudine fixed-dose combination, after PLHA networks filed a pre-grant opposition. In June 2008, India's patent office decided not to grant Boehringer Ingelheim a patent for the nevirapine paediatric syrup after a pre-grant opposition was filed. This set an important legal precedent and was followed by two further crucial rejections in 2009 for patents on the key ARVs tenofovir and darunavir, one of the most expensive ARVs today.

While several patent applications relating to tenofovir, darunavir and other key ARVs are still pending before the patent office, these rejections represent a major victory for access, as generic manufacturers have taken up the production of these medicines over time ensuring the lowest possible prices for these drugs. These decisions highlight the success and importance of Section 3(d) and opposition procedures in India's patent law to safeguard public health. Other countries in need of access to affordable essential drugs should build similar public health safeguards into their own patent law.

B) KEEP THE DOOR OPEN FOR COMPETITION, DESPITE PATENTS

When drugs are patented, and pharmaceutical companies fail to make patented medicines available and affordable to patients in developing countries, governments should make use of their right, under international trade laws, to issue compulsory licences to ensure generic competition, unless patent owners agree to voluntarily license their drug on reasonable terms. In both cases, royalties are paid to the patent holder.

COMPULSORY LICENSING

Compulsory licensing is one of the public health safeguards enshrined in the TRIPS Agreement, which allows a government to override a patent by issuing a licence to a third party to produce or import the drug. Issuing a compulsory licence (CL) has proven to bring prices down dramatically by opening up the market to competition and thereby increasing access.

The case of the CL issued by Thailand for LPV/r in January 2007 clearly illustrates this. Over the course of one year, the price for LPV/r in middle-income countries decreased by as much as 75%, from \$2,200 ppy to under \$900 in Thailand and \$550 in countries in the Clinton Foundation

Consortium. Similarly, a CL issued by Brazil for efavirenz in May 2007 brought the cost for the drug in Brazil down by almost 70%.

Even though issuing a CL is entirely in line with WTO rules, countries that take the step typically face immense direct and indirect retaliatory measures and pressure from developed country governments and the pharmaceutical industry. This can serve to discourage other countries that are considering issuing CLs. In a world in which medicines are becoming increasingly patented, CLs, including those for export, will be a critical mechanism to help ensure that essential medicines are affordable enough for people to access them and countries must feel supported in their right to increase access to needed medicines for their citizens.

This also means revising the current mechanism designed to allow the exporting of medicines under a compulsory licence to countries which have no manufacturing capacity, and therefore cannot 'simply' issue a CL and produce their own generic medicines. This mechanism, known as the August 30 Decision, was adopted by the World Trade Organization (WTO) in 2003.

Billed as an 'expeditious solution' that would open up access to medicines for millions, the Decision is in fact completely flawed. Canada was one of the first countries to enshrine the Decision in its national law – but it took five years from the time the Canadian Access to Medicines Regime (CAMR) became law for the first medicines to be exported from Canada under CL to reach patients in Africa.

While the fact that the drugs finally made it is obviously good news, it's quite clear that a process that takes so long, for just one drug, for just one country is not an adequate response. Given the global situation where 70% of patients in need of ART still do not have access to treatment, this procedure is simply not up to the task.

Canadian civil society is currently pushing for the CAMR to be reformed, but their efforts are being resisted by the pharmaceutical industry. Reform is needed at the international level at the WTO, and an in-depth review will be held at the next TRIPS Council meeting in October.¹⁸⁹ Yet a number of developed countries continue to oppose any review of the August 30 Decision, insisting there is not enough evidence to show that the mechanism is not working.¹⁹⁰

VOLUNTARY LICENSING

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

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

As an example, U.S. pharmaceutical company, Gilead Sciences, offered voluntary licence agreements for the production of tenofovir to any interested generic manufacturer in India with a number of clauses. The VL agreements stipulate that the generic manufacturers must purchase the active pharmaceutical ingredient from Gilead itself or from a Gilead licensee, instead of from a cheaper source, and that the manufacturers may not export the drug to several middle-income countries, including Brazil and China. This means that while competition among multiple manufacturers (licensees) within India has been taking place, Gilead maintains control over which countries are able to benefit from these lower prices, often keeping itself as the sole supplier source in these countries.

Crucially, all this was established by Gilead at a time when their patent

application on tenofovir was still awaiting a ruling from India's patent office. In 2006, Indian civil society organisations had filed pre-grant oppositions to the patent applications on the grounds that the drug consists of a previously-known substance and is therefore not patentable under India's Patents Act.

In September 2009, the Indian patent office subsequently declined to grant a patent for tenofovir disoproxil and tenofovir disoproxil fumarate and in July, the Brazilian patent office declined the patent for TDF. Gilead is now pursuing a new tactic to maintain its patent on TDF by filing divisional applications (a type of patent application which contains matter from a previously filed application) in the Brazilian and Indian patent offices.

STOP THE DELIBERATE CONFUSION OF QUALITY GENERIC MEDICINES AND COUNTERFEIT MEDICINES

Over the past few years there have been concerted attempts to subject developing countries to much stricter enforcement of intellectual property (IP) rules which go beyond the obligations required under the TRIPS Agreement and threaten the continued supply of affordable medicines to developing countries. As part of this push, there are proposals to introduce new procedures and laws against 'counterfeiting' – be it as national legislation, as a part of free trade agreements (FTAs), in multiple international fora such as the World Health Organization or the Council of Europe, or in the Anti-Counterfeiting Trade Agreement. Such initiatives threaten to hamper or prevent the trade in affordable generic medicines between developing countries.

Crucially, the use of the term 'counterfeiting' differs according to the context: in intellectual property

law, it refers to the protection of commercial trademarks, yet the way in which it has been commonly understood by many in public health, is as a reference to fake or falsely-labelled medicinal products that present a public health threat. This confusion has been exploited and the public health concerns about fake or falsely-labelled medicines used as an argument to push for stricter enforcement of intellectual property. Not only do these measures fail to address the public health problems, but they also actively interfere with and threaten access to medicines.

The dangers of overbroad IP protection are illustrated by the recent use of European Union customs rules, which are used to help enforce EU patents and trademarks. These rules have in fact prevented the timely access to life-saving medicines. Several shipments of generic medicines - including AIDS

drugs - have been detained in transit through European countries based on allegations of IP infringement, even though they are not protected by IP rights in the countries of export or import. This has affected the supply of essential medicines from manufacturers in India to patients in developing countries in Africa and Latin America. The EU customs rules should be amended to prevent this occurring again.

Another example is the Kenyan Anti-Counterfeiting Act which passed in December 2008, and which uses a definition of counterfeiting so wide that it includes all products that are copies of patented goods. This would also cover quality-assured and legally-produced generic medicines. The Act thus has the potential to seriously endanger access to generic medicines, such as those used by MSF and other treatment providers in Kenya. It is critical that the Act be revised. Three people living with HIV,

Continued above right 

❖ *Continued from below left*

supported by public health groups, have successfully obtained an interim injunction to stop key parts of the Act being implemented, pending a full hearing of a judicial review, on the grounds that the new legislation contravenes their 'right to life' under the Kenyan Constitution. At the 63rd World Health Assembly in May 2010 the Kenyan Minister of Health announced publically that the Ministry of Health had not been consulted on the draft law which has hampered efforts to improve access to medicine in the country.^{11,22} There have been recent encouraging statements from the Kenyan Government that this legislation must not affect access to medicines. However the Act has not yet been amended.

In a worrying trend, there are attempts to introduce similar legislation in Uganda. Public health organisations there are concerned that the country's draft Counterfeit Goods Bill 2009 may also threaten access to generic medicines if passed in its present form.

One major problem that is not addressed by the use of the excessively general term 'counterfeit', and which MSF teams face in many countries, is posed by substandard drugs. These are drugs from originator companies as well as from generic producers that do not meet international standards of quality set for them.

To date though, the focus of the response to these questions has been placed on protecting commercial interests, rather than addressing serious public health issues.

This has meant diverting attention from what needs to be done.

In direct response to these concerns, WHO member states agreed at the World Health Assembly in May 2010 to set up an intergovernmental working group to ensure WHO takes a public health perspective in its efforts to ensure the availability of quality, safe, efficacious and affordable medicines, excluding trade and intellectual property considerations. It is important that the working group acts quickly to address these issues, and that proposals for greater protection of commercial interests that threaten access to medicines are rejected.

To learn more about the fatal confusion between legitimate generic medicines and illegal fakes, please watch MSF's animation at <http://vimeo.com/11709053>

C) POOL PATENTS AND TAKE THE PLUNGE FOR AFFORDABLE TREATMENT

Company-led 'access' schemes have proven to be minimally effective. While most multinational companies today do offer discounts through tiered pricing, the data contained in *Untangling the Web of Antiretroviral Prices* clearly shows that in the absence of generic competitors, manufacturers enjoying a monopolistic situation do not reduce prices significantly enough to make medicines affordable for developing countries. Also, countries that are classified as 'middle-income' such as Brazil, Thailand, China or Colombia, are often left out of the discount scheme altogether or are offered only minimal discounts. Primarily the threat of losing a patent or having a patent barrier removed is what makes companies respond and reduce prices. In some cases, generic competition is only possible through governments issuing compulsory licences.

There is one way companies could act to make a difference to improve access to medicines in the developing world, however. The international drug purchase facility UNITAID has recently established a Medicines Patent Pool for antiretrovirals. Instead of having patents act as barriers, companies, researchers or universities license the patents on



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their inventions to one entity: the Medicines Patent Pool.

In this way, any generic company that wants to use the patented inventions can seek a licence from the pool, under pre-determined licensing terms, in exchange for the payment of royalties to the patent holder. The licensee could then produce generic versions of the patented inventions and export them to countries covered by the licence.

In order to ensure a sufficiently attractive, large market for potential producers, the licences must be valid for a wide geographical area which includes all developing countries. This would result in competition between producers, bringing drug prices down.

Continued on page 15 ❖

AIDS TREATMENT DELAYED, DEFERRED, DENIED

The past decade is testimony to the fact that treating AIDS in developing countries is feasible, saves lives and rebuilds devastated communities. But donors are now starting to shift their support away from HIV/AIDS, and MSF has seen the tangible effects this funding retreat is already having: care rationed because of limited treatment slots, treatment scale-up halted for those in urgent need, and an even more distant promise of universal access.

The decade ahead of us should not be spent undoing the hard-won advances. The AIDS funding retreat will have the following consequences:

1. Limiting treatment slots means choosing who lives or dies:

Because of funding cuts, treatment providers are being forced to turn people in need of treatment away from clinics in some countries, having been forced by lack of funds to only enroll new patients on treatment when others die or default.

2. Delaying or deferring treatment encourages transmission, illness and death:

Providing ART earlier lets people live healthier lives, reduces the incidence of opportunistic infections, and decreases the need for resulting care and hospitalisation. It also reduces the number of people lost to follow-up before they start treatment. With increasing evidence that treatment is prevention, failing to provide treatment earlier also allows the virus to spread.

3. Failing to ensure a stable drug supply means viral load shoots through the roof:

Reduced funding leads to volatility in drug supplies, which can lead to dangerous treatment interruptions. Without the virus being constantly suppressed through ARVs, people can rapidly fall ill again and die, and drug-resistant strains can spread.

4. Breaking the promise of ART means people won't come forward to get tested:

People came forward to get tested because they knew treatment was available should they test positive. If people in need to treatment come to believe this is no longer true, the hard-won progress on encouraging people to know their status will come undone, with potentially disastrous ramifications.

5. Slowing AIDS efforts means the number of kids infected with HIV will rise:

Children's needs have consistently lagged behind adults for AIDS treatment. Badly needed diagnostic tests and drug options for children will be even less of a priority in a reduced funding environment. Improved WHO-recommended protocols to prevent transmission of the virus from mother-to-child (PMTCT) will also likely fall by the wayside, meaning the needless infection of newborn children.

6. Slowing down the integration of HIV and TB care means patients will slip through the cracks:

TB remains the number one killer of people living with HIV/AIDS, and providing integrated care for both TB and HIV/AIDS is the most effective way to tackle this dual epidemic. But such integration has only barely begun in endemic countries, and waning support for HIV/AIDS care will slow it even further.

7. Choosing between maternal & child health or AIDS means making a false choice:

AIDS is the main killer of women of childbearing age and over 40% of deaths of children under five years in six southern African countries are because of AIDS. Addressing AIDS creates positive knock-on effects in other health areas. More funding should be allocated to global health rather than withdrawing support from one area to fund another.

8. Calling an end to decentralisation of care mean it's harder to reach people in urgent need:

Bringing AIDS treatment close to where people live reaches more people in need and lowers the rate of patients lost to

'Donors have been shifting their focus from AIDS to other diseases, where there is a sense that more lives can be saved more cheaply. At a time when we should be scaling up to meet the AIDS challenge, in other words, we are dialling back. In our global war on AIDS, the international community is on the verge of snatching defeat from the jaws of victory.'

*UN Secretary General Ban Ki-Moon,
14 June 2010*

follow-up. This is a particularly effective way to scale up ART in areas that are hard hit by severe health worker shortages. But without support, it will not be possible to expand this successful model.

9. Continuing to use drugs with more side effects means relegating patients to second-class care:

WHO has recommended that less-toxic drugs be used in first-line treatment, as part of the effort to close the treatment gap between rich and poor countries. This means substituting stavudine, with significant side effects, for tenofovir (TDF), or zidovudine. Despite prices falling, the cheapest TDF-containing regimen is still more expensive than older alternatives. However, using TDF decreases the cost of managing side effects through medical care and/or hospitalisation, thereby proving more cost-effective in the long run. The provision of less-toxic medicines cannot be prioritised if funds are short.

10. Cutting back on funding for treatment means sacrificing long-term survival:

AIDS is a lifelong disease and patients inevitably need to be switched to newer regimens as drug resistance develops over time. But treatment failure is a hidden problem because of a lack of affordable and accessible viral load testing. Further, newer medicines are much more expensive. This means that patients are less likely to be switched when necessary, and even less so when there is reduced funding for AIDS treatment.

Donors are walking away from AIDS when 10 million people are still waiting for treatment. Help us stop the U-turn on AIDS. <http://aids2010.msf.org>

❖ *Continued from page 13*

The Medicines Patent Pool has the potential to help increase access to ARVs in three key areas:

1. By fostering competition among multiple manufacturers, bringing prices down for newer medicines and increasing access, it will help mitigate the impact of the TRIPS patent regime, especially for the newer ARVs patented in manufacturing countries such as India and Brazil;
2. It will help facilitate the creation of needed fixed-dose combinations, where otherwise patents on the individual drug compounds stand in the way; and
3. It will further facilitate the development of paediatric ARV formulations and combinations, by eliminating patent barriers in developing countries.

MÉDECINS SANS FRONTIÈRES IS CALLING FOR ALL PATENTS ON THE FOLLOWING ANTIRETROVIRALS (AND COMBINATIONS THEREOF) TO BE PUT IN THE MEDICINES PATENT POOL:

lopinavir, ritonavir (Abbott);	efavirenz, raltegravir (Merck);
nevirapine, tipranavir (Boehringer Ingelheim);	SPI-452 (Sequoia);
atazanavir, didanosine (Bristol-Myers Squibb);	darunavir, etravirine, rilpivirine (Tibotec / Johnson & Johnson);
emtricitabine, GS-9350, elvitegravir, tenofovir disoproxil fumarate (Gilead);	abacavir, fosamprenavir, lamivudine, maraviroc, S/GSK1349572 (ViiV)

MSF has identified a list of medicines whose patents should be included in the pool, and a list of needed fixed-dose combinations that it is hoped the pool will help deliver. However, the pool will be voluntary, so crucially, the success of the patent pool depends on companies'

willingness to include their patents in the pool for use in all developing countries, and on generic manufacturers' interest in those licences. With the Foundation entrusted with running the patent pool now officially established, companies have no excuses not to act.

CONCLUSION

Looking back upon the first decade of AIDS treatment in developing countries shows key successes. Four million people on treatment are alive today, many of whom would have died without ARVs long ago. The case has thus been proven that AIDS treatment is entirely feasible in resource-limited settings. However, with six out of 10 people in need of treatment still not receiving it and with projections of up to 50 million people in need of treatment in roughly 20 years, it is clear that treatment scale up must occur at a faster pace.

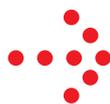
At the same time, steps must be undertaken to ensure that people in developing countries are receiving the optimal monitoring and treatment that supports their long-term survival, comparable to their counterparts living with HIV/AIDS in wealthy countries. This means securing access to needed monitoring tools, while providing patients both with a robust first-line regimen that has few side effects, as well as ensuring there are treatment options for when patients show signs of drug resistance and need to switch to a second- or third-line combination.

Although prices for certain key newer medicines have come down significantly because of competition among generic manufacturers and

increased demand, overall prices for newer drugs remain unaffordable for developing countries and out of reach of national treatment programmes.

Countries must be supported in their use of flexibilities in international trade rules to help bring prices of newer drugs down more systematically and speedily. This is necessary so that the growing number of people in need of newer and more potent drugs have immediate access once they require them. Pharmaceutical companies should participate in the Medicines Patent Pool, so that needed formulations can be made available to developing countries more swiftly and at much more affordable prices.

HIV/AIDS must continue to be treated as the emergency it is. Funding levels must be increased to take on the massive task of providing sustained AIDS treatment in developing countries. New financing mechanisms, such as financial transaction taxes including currency transaction levies, should be introduced to help raise much needed additional sustainable and predictable resources, part of which must be dedicated to global health. The worrying trend of treatment providers needing to scale back ART at a time when they should be scaling up must be countered with sustained and reaffirmed commitment by leaders and donors to universal access to HIV/AIDS treatment.



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.'

More commonly known as the WHO prequalification list, the project 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.

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

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

QUALITY OF DRUGS IN THE DATA PROVIDED IN UNTANGLING THE WEB

Manufacturers who have at least one WHO prequalified antiretroviral formulation were invited to participate in this publication.

But not all the products listed in this report have been prequalified by WHO and only some of them are used by

MSF in its own projects. Products included in the List of Prequalified Medicinal Products (as of April 2010), including the ones approved by Health Canada, the European Medicines Agency (EMA) through article 58, U.S. FDA or tentatively approved by U.S. FDA, appear in **bold** in the tables of drug prices.

Please consult the WHO website (<http://mednet3.who.int/prequal>) for the latest list of prequalified products and for information on the status of dossier assessment.

Questionnaires were sent to both originator and generic companies manufacturing antiretrovirals (ARVs), requesting information on prices for developing countries, restrictions that apply to each of the prices quoted (eligibility criteria), and any additional specificity applicable to the quoted prices. The data were collected up to May 2010.

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 listed on the WHO List of Prequalified Medicinal Products on the date of the initial request for information were included in this publication. The initial questionnaires were sent in the middle of April 2010.

Only generic manufacturers who provided prices for their products are included in this document. Aspen Pharmacare was invited to contribute to this publication; however, the company has chosen not to provide prices, and as such will not be included in this document. Similarly, Macleods and Emcure have chosen not to provide information for this publication.

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

- The information on prices given in this publication only relates to ARVs. It does not include other costs linked to antiretroviral treatment, such as diagnosis, monitoring or treatment of opportunistic infections. For information on the prices of these products, please refer to 'International Drug Price Indicator Guide'¹⁹ and for paediatric drugs, 'Sources and prices of selected medicines for children'.²⁰
- The manufacturers provide the prices listed in this publication. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower after negotiations. The document should not be viewed as a manufacturer's price list, and procurement agents are advised to contact manufacturers directly to confirm prices.

- Companies use different trade terms (known as incoterms).²¹ 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. Prices in the publication have not been adjusted to incorporate the different terms. In 2005, the U.S. General Accountability Office demonstrated that these differences do not undermine their essential comparability.

- Originator and some generic companies have different eligibility criteria for differential pricing for countries and entities, meaning not all countries and entities can access the price that is mentioned in this guide. The different categories of prices are detailed on the drug profile pages. More detailed information on the different eligibility criteria is provided in Annexes 2-10.

- The Clinton Foundation's Health Access Initiative negotiates prices for ARVs and diagnostic tests with generic companies on behalf of national AIDS programmes included in their consortium. The Clinton Foundation has reached agreements with seven ARV manufacturers to lower the prices of 38 different ARV formulations, both paediatric and adult. The current price list, as of April 2010, can be found in Annex 13.

- 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 List of Prequalified Medicines is updated regularly, the list should be consulted for up-to-date information regarding quality. <http://apps.who.int/prequal/>

NOTE: An online version of *Untangling the Web of Antiretroviral Price Reductions* launched in January 2010. The online version reproduces the features of *Untangling the Web* in a clear, user-friendly and free-flowing design. It is updated regularly.

You can access it at <http://utw.msfacecess.org>

HOW TO READ THE DRUG PROFILES

There are separate drug profiles for each of the single antiretrovirals (ARVs), fixed-dose combinations (FDCs) and co-packs containing two or three ARVs. Each drug profile contains the following sections:

GENERAL INFORMATION:

General information on the history of the product, brand name, date of approval by the U.S. FDA and relevant WHO guidance.

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

All prices are quoted in United States Dollars (US\$). Currency conversions were made on the day the price information was received using the currency converter site www.oanda.com.

The annual cost of treatment per patient year (ppy) has been calculated according to the WHO dosing schedules,⁸ multiplying the unit price (one tablet, capsule or millilitre) by the number of units required for the daily dose, and by 365. The price of the smallest unit (i.e. price per capsule, tablet, etc.) is included in brackets. Where no WHO guidelines exist for a product, the dosage used is the U.S. FDA approved dosage.²³

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

For paediatric treatments, prices are calculated for a 10 kg child using recommended dosing based on weight bands, as per the WHO treatment guidelines.¹³⁷ 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 10 kg child, only the unit price is indicated. For paediatric FDCs, the dosages used for the calculation are those recommended by the Paediatric Antiretroviral Working Group at WHO.¹³⁷

ACCESS TO PRICE DISCOUNTS – CATEGORIES 1 AND 2

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

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

The WHO List of Prequalified Medicinal Products is a list of manufacturers and suppliers who meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis medicines. Products included in the WHO List of Prequalified Medicinal Products for Antiretrovirals (as of April 2010) 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 Program website as this list is updated regularly (<http://apps.who.int/prequal/>).

The Clinton Foundation's HIV/AIDS Initiative negotiates with several manufacturers for reduced prices for almost 38 different ARV formulations for countries in their pooled procurement consortium. Manufacturers who have a product included in the most recent price announcement are indicated by a (CF) in the header of the table. Further details of the specifics of the product can be found in Annex 13.

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

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

If a generic product included in the WHO List of Prequalified Medicinal Products is available, the graph shows the lowest-priced generic product that is included in the list. If no generic product is included in the WHO List of Prequalified Medicinal Products, the lowest-priced product is considered in the graph, regardless of quality status.

SPOTLIGHT ON ACCESS ISSUES – A LOOK AT PATENTS AND PAEDIATRICS

The most salient issues related to access to each product is summarised here. The focus is on the availability of products, their affordability and their adaptability for the developing world. Special comment has been included when appropriate with regard to patents and paediatrics.

MARAVIROC (MVC)

GENERAL INFORMATION

- Therapeutic class: chemokine co-receptor 5 (CCR5) antagonist (entry inhibitor).
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced adult patients infected with only CCR5 tropic HIV-1 detectable strains, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.²⁵
- Originator company and product brand name: Pfizer, Selzentry. In April 2009, Pfizer and GlaxoSmithKline jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approved by the U.S. Food and Drug Administration (FDA): August 2007.¹⁷
- Not included in the WHO Model List of Essential Medicines (EML).²⁶
- The basic patent was applied for by Pfizer in December 1999²⁷ and is due to expire in 2019. In May 2001, Pfizer applied for an additional patent more specifically related to crystalline maraviroc.²⁸

PRICE INFORMATION

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

SPOTLIGHT ON ACCESS ISSUES

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

The recommendation is for patients to have a tropism test to look for this co-receptor prior to treatment. In developing countries, where basic laboratory monitoring is not always available, the reality of this type of testing being available is limited.

Today, this test is not widely available and is expensive, at approximately US\$ 1,900.²⁹

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

Patents

Pfizer obtained a patent in India in 2007.³⁰

This patent blocks the manufacture of generic formulations of MVC in India, limiting the much-needed competition that historically has been shown to lead to price reductions.

Pfizer has applied for product patents and patents for the crystal form in Brazil, South Africa, India, China, ARIPO³¹ and OAPI countries.³²

To date, patents on the crystal form have been granted in India, China, and ARIPO and OAPI countries.

Paediatrics

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



GENERAL INFORMATION

- Therapeutic class: fusion inhibitor.
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced adult patients who have evidence of viral HIV-1 replication despite ongoing antiretroviral therapy.³³
- Originator companies and product brand name: Roche and Trimeris, Fuzeon.
- First approved by the U.S. Food and Drug Administration (FDA): March 2003.¹⁷
- Not included in the WHO Model List of Essential Medicines (EML).²⁶
- The basic patent on enfuvirtide was applied for by Duke University in June 1994,³⁴ and is due to expire in 2014. Duke researchers founded the pharmaceutical company Trimeris,

which began development of enfuvirtide (previously called T-20) in 1996. In 1999, Trimeris entered into partnership with Hoffmann-La Roche to complete the development of the drug. Chiron also owns patents related to processes for producing enfuvirtide,³⁵ which expired in 2005, but protection has been extended until 2010 in some European countries. A licensing agreement was established between Roche and Chiron in 2004.³⁶

PRICE INFORMATION

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

SPOTLIGHT ON ACCESS ISSUES

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

Enfuvirtide is formulated as an injection and requires the patient or caregiver to learn the technique of reconstituting powder vials with sterile water. Since the vials are formulated for single use, it requires the patient or caregiver to accurately syringe out the required

dose and volume. This is not adapted for use in resource-limited settings, and the current price in the developed world of nearly US\$ 25,000 per patient per year is prohibitive for many developing countries that may have a need for this product.³⁷

In Brazil, enfuvirtide is available at \$12,812 ppy.¹²⁹

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

Patents

Trimeris filed for patents related to methods for synthesizing enfuvirtide in developing countries such as China and Brazil, which may run until 2019.³⁸

The patent was granted in China.³⁹

Paediatrics

The drug is approved for use in children over six years of age.

RALTEGRAVIR (RAL)

GENERAL INFORMATION

- Therapeutic class: integrase inhibitor.
- Listed in the WHO guideline as potential third-line drug.⁸
- Indicated for treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.⁴⁰
- Originator company and product brand name: Merck, Isentress.
- First approved by the U.S. Food and Drug Administration (FDA): October 2007.¹⁷
- Not included in the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 752 million⁴¹; 2008: \$361 million; 2007: \$41 million.⁴²
- The basic patent was applied for in October 2002 by the Institute for Research in Molecular Biology (IRBM), Pomezia, Italy, one of Merck's research sites.⁴³ The patent is due to expire in 2022. In 2005, Merck and IRBM applied for another patent on the potassium salt of RAL which can run up to 2025.⁴⁴

PRICE INFORMATION

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

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

	Daily dose	Merck	
		Category 1 countries	Category 2 countries
Who can access this price?		See annex 2 & annex 10	
RAL 400mg tablet	2	1113 (1.525)	Not Available

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.

RAL, unlike most protease inhibitors (PIs), does not require boosting with ritonavir (RTV). This new drug option will be very important for patients who are treatment-experienced and may already be resistant to multiple antiretroviral agents.

In December 2009, WHO released new recommendations which for the first time call for a third-line therapy. As human studies are ongoing, the drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.⁹

There is no generic raltegravir available.

RAL pricing for category 1 countries (see annex 10) is extremely high and unaffordable for developing countries. RAL pricing for category 2 countries is still unknown. In Brazil, however, raltegravir is already included in the national treatment guidelines and around 3,000 patients are on raltegravir in the country. The cost per patient per year stands at \$5,870.¹²⁹

Patents

Merck and IRBM applied for patents in many developing countries with generic drug manufacturing capacity, such as Brazil, China, India and South Africa. IRBM was granted a patent in India in December 2007⁴⁵ which will expire in 2022.

Generic competition to reduce the price of the medicine will therefore only be possible through voluntary licences issued by the patent holder, or through compulsory licences issued by the government.

Paediatrics

The safety and efficacy of RAL in patients under 16 years of age have not been established. Paediatric studies are ongoing in children from four weeks old.

EFAVIRENZ (EFV)

GENERAL INFORMATION

- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Indicated for first- and second-line for adults, adolescents and children.^{18, 137}
- Originator companies and product brand names: Bristol-Myers Squibb (BMS), Sustiva; or Merck, Stocrin.
- First approval by U.S. Food and Drug Administration (FDA): September 1998.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 1.277 billion; 2008: \$1.149 billion; 2007: \$956 million; 2006: \$791 million; 2005: \$680 million; 2004: \$621 million; and 2003: \$544 million.^{46, 47, 48, 49, 50}
- The basic patent on EFV was filed in 1993 by Merck, and is due to expire in 2013.⁵¹ Subsequently, Merck filed for patent applications related to crystallized forms, due to expire in 2018.⁵²

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet/capsule/suspension dose. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

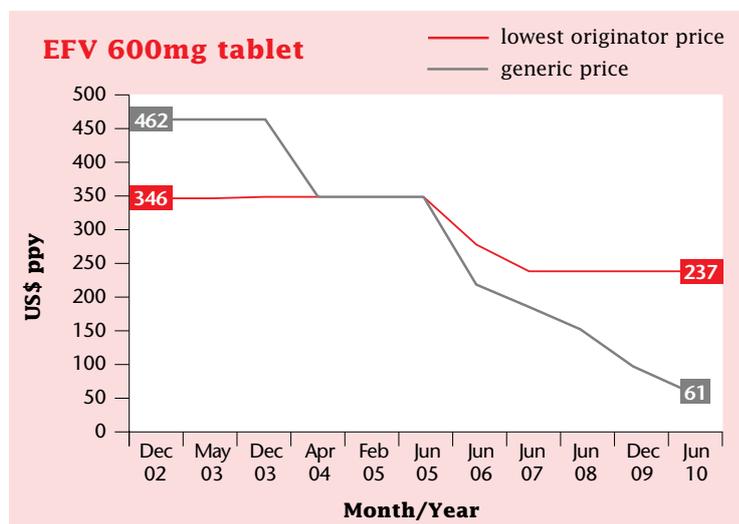
	Daily dose	Merck		Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy	Strides (CF)
		Category 1 countries	Category 2 countries						
Who can access this price?		See annex 2 & annex 10		No restrictions					
EFV 30mg/ml suspension	-	(0.094/ml)	(0.151/ml)						
EFV 50mg capsule	-			(0.083)					
EFV 50mg tablet	-	(0.120)	(0.210)				(0.083)		
EFV 100mg capsule	-			(0.150)					
EFV 200mg capsule	3			130 (0.119)	134 (0.122)	152 (0.139)		118 (0.108)	
EFV 200mg tablet	3	394 (0.360)	821 (0.750)				146 (0.133)		110 (0.100)
EFV 600mg tablet	1	237 (0.650)	657 (1.800)	73 (0.200)	79 (0.217)	82 (0.225)	61 (0.167)	91 (0.250)	62 (0.170)

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

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

As of April 2010, there were seven generic sources of EFV 600mg tablet listed on the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

Since 2002, the originator price has decreased by 32%, while generic prices have dropped by 87%.



SPOTLIGHT ON ACCESS ISSUES

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

In its new 2010 guidelines, WHO recommends the use of EFV - in combination with two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF) – as a preferred first-line antiretroviral treatment.⁹

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

Its price, however, remains high, particularly for countries included in Merck's second pricing tier (see annex 10), where the price of EFV 600mg tablet exceeds by more than 10 times the price of the generic version.

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

Patents

Generic competition from a number of Indian manufacturers has brought the price of EFV down significantly. However, EFV remains expensive in countries where Merck holds patents that block the production and sale of generics.

In countries where EFV is patented, governments and civil society groups have taken various measures to ensure generic competition and lower prices, including:

- In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government is now purchasing EFV at US\$ 106 per patient per year (ppy), which is considerably lower than the previous price of \$511 ppy.^{53,54}
- In May 2007, Brazil, after numerous unsuccessful negotiations with Merck, issued a compulsory licence to import more affordable generic versions of EFV from India. At the time, the price of EFV in Brazil was \$580 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a generic version prequalified by WHO for \$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched the national generic version for use in the Brazilian health system.⁵⁵
- 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 (ALP), acting on behalf of the Treatment Action Campaign (TAC), to file a complaint before the Competition Commission in November 2007. As a result, Merck recently agreed to license its product to other producers, opening the opportunity for generic competition in South Africa, where six suppliers now market efavirenz or efavirenz – containing combination products.⁵⁶
- In India, a patent for the process of preparing form 1 of crystalline EFV was granted in June 2005.⁵⁷ Even though Merck does not hold a product patent for EFV, this recently granted process patent

appears to protect a key process for manufacturing EFV, and could therefore have an impact on generic production of EFV in India. This patent has therefore been opposed by Indian civil society organisations using the post-grant opposition procedures enshrined in India's patent law.⁵⁸

In addition, Gilead⁵⁹ and BMS have filed patent applications related to combinations of EFV with other ARVs. In particular, BMS's efforts to receive a patent for the once-a-day pill EFV/FTC/TDF⁶⁰ will have an impact on access to improved first-line ARV treatment in the developing world. In India, the patent office has already rejected Gilead's application,⁶¹ as combinations of known molecules are not patentable under India's patent law.

Paediatrics

Despite having received U.S. FDA approval for use in adults in 1998, there is still no established dosing of EFV for children less than three years of age. There is an urgent need to establish the dosing of EFV for this age group.

In early 2008, BMS, which markets EFV in Europe, discontinued the manufacture of the 100mg capsule, further limiting options for paediatric patients. The oral solution, while allowing more flexibility in dosing, must be discarded 30 days after being opened, and is not interchangeable on a mg per mg basis with the solid dosage forms. The bioavailability of the oral solution is less than 70% of the oral dosage forms, and hence a larger dose is required to obtain the same blood levels.

ETRAVIRINE (ETV)

GENERAL INFORMATION

- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Listed in the WHO guideline as potential third-line drug.⁸
- Approved by U.S. Food and Drug Administration (FDA) for treatment-experienced adult patients who have evidence of resistance to an NNRTI and other antiretroviral agents.⁶²
- Originator company and product brand name: Tibotec, Intelence.
- First approved by the U.S. FDA: January 2008.¹⁷
- Not included in the WHO Model List of Essential Medicines (EML).²⁶
- The basic patent on etravirine was applied for by Janssen Pharmaceutica in 1999 and is due to expire in 2019.⁶³ In 2006, Tibotec applied for subsequent patents related to novel series of bisaryl substituted pyrimidine derivatives. Both Janssen Pharmaceutica and Tibotec are now part of Johnson&Johnson.^{64,65}

PRICE INFORMATION

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

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

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

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations which for the first time call for the need for third-line therapy. As many studies are ongoing, the drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.⁹

Etravirine was approved by the U.S. FDA in January 2008, and received marketing approval by the EMA in August 2008. It has not yet been approved by any developing country health authority. However, the product is available through a pre-approval access program which is managed by Aspen Pharmacare.

The price of etravirine has now been revealed for the first time by Tibotec. At US\$ 913 ppy, this price is prohibitive for the developing countries. There is no generic version of this drug available.

Patents

Patents have been applied for widely in the developing world, including in Africa. Janssen Pharmaceutica obtained the molecule patent in India⁶⁶ and China.³⁹

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

Paediatrics

Etravirine is not approved for use in children today. A waiver of paediatric studies from birth to two months was granted by the EMA on grounds that the medicine does not represent significant therapeutic benefit over existing treatments.⁶⁷

NEVIRAPINE (NVP)

GENERAL INFORMATION

- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Indicated for first- and second-line for adults, adolescents and children.^{8,137}
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune.
- First approval by U.S. Food and Drug Administration (FDA): June 1996.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2007: US\$ 412 million; 2006: \$370 million; 2005: \$386 million; 2004: \$378 million.^{68,69,70,71} After 2007, there are no sales figures quoted in the company's annual report.
- The basic patents on NVP were applied for by BI in November 1990, and are due to expire in November 2010.⁷² BI also applied for a patent on the hemihydrate form of NVP, used in the suspension in 1998, which is due to expire 2018.⁷³ Additionally, BI applied for a patent on the extended-release formulation of nevirapine in 2008, which is due to expire in 2028.⁷⁴

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet/suspension dose. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

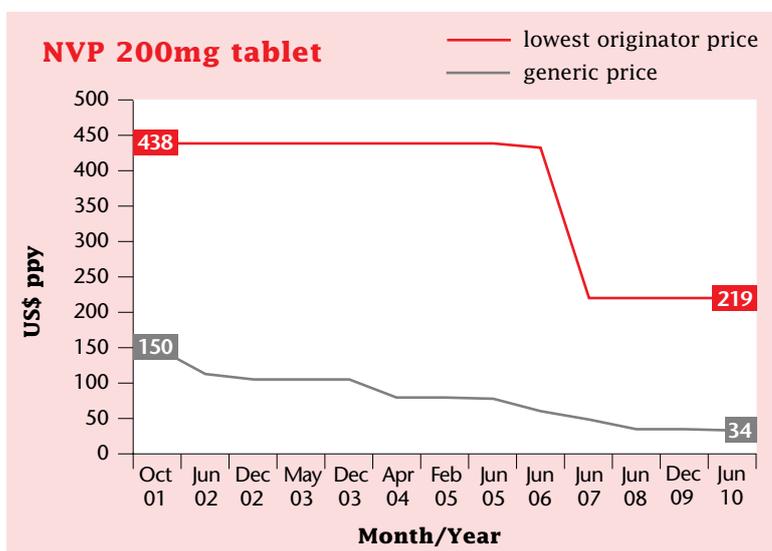
	Daily dose	BI		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Huahai	Matrix (CF)	Ranbaxy (CF)	Strides
		Category 1 countries	Category 2 countries							
Who can access this price?		See annex 2		No restrictions						
NVP 10mg/ml suspension	20ml	380 (0.052/ml)	533 (0.073/ml)	66 (0.009/ml)	73 (0.010/ml)					
NVP 200mg tablet	2	219 (0.300)	438 (0.600)	39 (0.054)	34 (0.046)	37 (0.050)	34 (0.047)	39 (0.054)	39 (0.053)	37 (0.050)

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

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

As of April 2010, there were 10 generic sources of NVP 200mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

While it was a positive result that the originator company dropped its price by 50% in 2007, the generic price has decreased by almost 80% since 2001, and today is approximately 16% of the originator price.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

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

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

Patents

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

However, after India introduced patent protection for pharmaceutical products in 2005, BI applied for a patent on the hemihydrate form of NVP, which relates to the paediatric suspension. Civil society groups in India filed a pre-grant opposition to BI's patent application in May 2006. In June 2008, the patent application on the NVP hemihydrate was rejected by the Indian patent office, allowing for unrestricted competition on the paediatric formulation. This constituted an important victory for Indian civil society, as this was the first patent application related to a HIV medicine to have been rejected as a result of a pre-grant opposition process, in accordance with the 2005 Indian Patents Act.⁷⁵

Paediatrics

NVP is approved for use and is widely-used in children.

With the increased prevalence of TB/HIV co-infection, there is a need for further studies into the interactions between NVP and the TB drugs rifampicin and rifabutin in children.²⁹

BI has a NVP donation programme for the prevention of mother-to-child transmission (PMTCT). This, however, does not cover treatment for children. When BI announced a reduction of 50% for NVP in mid 2007, it did not include the NVP 10mg/ml solution, where a price drop would have had a considerable impact. It therefore costs more to treat a 10kg child with NVP than an adult.

Generic manufacturers have been developing triple fixed-dose combinations including NVP, but today only three paediatric triple FDCs that include NVP are included in the WHO Prequalification List of Medicinal Products.

A new formulation of NVP 20mg scored tablet is suggested by the WHO Paediatric Antiretroviral Working Group for the new WHO PMTCT guidelines for infant prophylaxis.¹³⁷

ABACAVIR (ABC)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line: for adults, adolescents and children.^{8,137}
- Originator company, and product brand name: GlaxoSmithKline (GSK), Ziagen. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): December 1998.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product for 2009: US\$ 160 million; 2008: \$175 million; 2007: \$215 million; 2006: \$230 million; 2005: \$268 million; 2004: \$290 million.^{77, 78, 79, 80, 81, 82}
- The basic patents on ABC were applied for by GSK in 1989⁸³ and 1990,⁸³ and these are due to expire in 2009 and 2010, respectively. GSK subsequently applied for an additional patents related to new intermediates in 1995,⁸⁴ to on the hemisulfate salt of ABC in 1998⁸⁵ and to compositions of ABC particularly relevant for paediatric use in 1999, which⁸⁶ are due to expire in 2015, 2018 and 2019, respectively.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet/dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

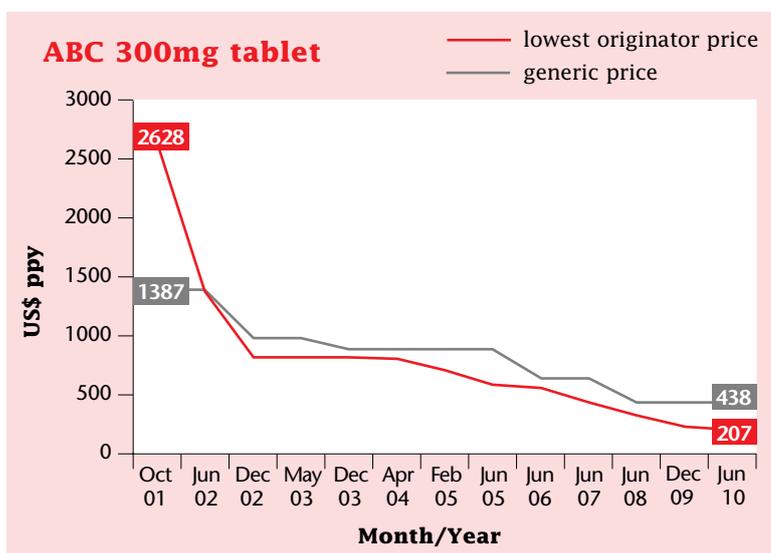
	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		See annex 2	No restrictions					
ABC 20mg/ml oral solution	10ml	230 (0.063/ml)	212 (0.058/ml)	113 (0.031/ml)				
ABC 60mg tablet	4		153 (0.105)	134 (0.092)		183 (0.125)		540 (0.370)
ABC 300mg tablet	2	438 (0.600)	243 (0.333)	207 (0.283)	256 (0.350)	219 (0.300)	274 (0.375)	

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

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

As of April 2010, there were four generic sources of ABC 300mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 68%, while the generic price has decreased by 92%.



Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r), and simplified NRTI options are recommended. Abacavir (ABC) and didanosine (ddI) are no longer recommended as one of the NRTI backbones in second-line therapy.⁹

Even though the price of ABC has fallen by almost 92% in generic pricing since 2001, the current lowest generic price is more than twice the lowest price of tenofovir (TDF) or zidovudine (AZT). Additionally, GSK's differential pricing structure (see annex 2) excludes some low- and middle-income countries that are not funded by the Global Fund. The current price in the developed world of \$4,600 ppy is prohibitive for many developing countries that need to access the product.⁸⁷

Patents

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

However, patents have been granted in China⁸⁹, and GSK has applied for patents on the hemisulfate salt of ABC and on compositions of ABC particularly relevant for paediatric use in India. GSK withdrew its patent application on the hemisulfate salt of ABC in October 2007 after it was opposed by civil society groups in July 2006 in a pre-grant opposition procedure.⁸⁸ Nevertheless, the patent more specifically related to paediatric formulations was granted in December 2007.⁸⁹ This patent raises concerns over the continued generic availability of the ABC paediatric formulation, which is an important option for young children with HIV/TB co-infection.

Paediatrics

ABC is approved for use in children.

There is a liquid formulation and today, two generic sources of paediatric ABC 60mg tablet are included in the WHO List of Prequalified Medicinal Products.

ABC will continue to be an important drug for HIV/TB co-infected small children, who have limited choices of ARVs because of drug interactions between TB drugs and nevirapine (NVP), and because of the lack of dosage data on efavirenz (EFV) for children under three.

Today, once-daily dosing of ABC is only recommended for patients over 12 years of age; more studies are needed to confirm the safety of daily dosing of ABC in children.⁹⁰

DIDANOSINE (ddl)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for second-line for children.¹³⁷
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Videx/Videx EC.
- First approval by U.S. Food and Drug Administration (FDA): October 1991 for chewable tablets; October 2000 for enteric-coated capsules.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2005: US\$ 174 million; 2004: \$274 million; 2003: \$354 million. After 2005, there are no sales figures listed in the company's annual report.⁴⁹
- The basic patent on ddl filed in 1985 by the National Institutes of Health (NIH), a U.S. government research institute, has expired, but BMS holds patents on improved formulations in some countries, which run until 2012 and 2018.⁹¹

PRICE INFORMATION

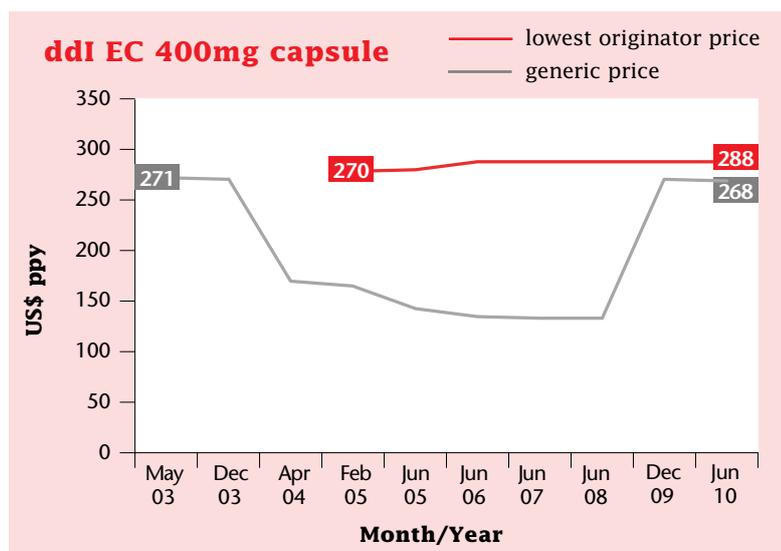
Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/capsule/dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	BMS		Aurobindo	Cipla	Ranbaxy
		Category 1 countries	Category 2 countries			
Who can access this price?		See annex 2 & annex 7		No restrictions		
ddl 2g powder for reconstitution (final concentration 10mg/ml)	12ml	276 (12.590/2g)	308 (14.057/2g)	88 (4.000/2g)		
ddl 25mg tablet	5	212 (0.116)	429 (0.235)		115 (0.063)	228 (0.125)
ddl 50mg tablet	-	(0.158)	(0.235)		(0.079)	(0.115)
ddl 100mg tablet	4	311 (0.213)	364 (0.249)	194 (0.133)	188 (0.129)	242 (0.166)
ddl 125mg enteric-coated capsule	1			110 (0.300)		
ddl 150mg tablet	-	(0.308)	(0.345)	(0.225)	(0.167)	
ddl 200mg tablet	-			(0.267)	(0.257)	
ddl 200mg enteric-coated capsule	-			(0.383)		
ddl 250mg enteric-coated capsule	1	223 (0.611)	249 (0.683)	170 (0.467)	103 (0.283)	
ddl 400mg enteric-coated capsule	1	288 (0.789)	322 (0.881)	256 (0.700)	132 (0.363)	

Continued overleaf ❖

Didanosine (ddl) continued



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

As of April 2010, there was one generic source of ddl 400mg enteric-coated capsule included in the WHO List of Prequalified Medicinal Products. Its price is shown here.

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r), and simplified NRTI options are recommended. Abacavir (ABC) and didanosine (ddl) are no longer recommended as one of the NRTI backbones in second-line therapy.⁹

BMS's differential pricing structure limits the prices quoted above to sub-Saharan Africa and low-income countries. This structure leaves some countries paying more than US\$ 3,600 per patient per year for ddl 400mg enteric-coated (EC) capsules, which is prohibitive for many of these countries.⁸⁷

In 2007, BMS announced its plans to restructure the company into a BioPharma company. The plans include reducing the number of brands in the company's mature products portfolio by 60% between 2007 and 2011 and reducing of the company's manufacturing facilities by more than 50% by the end of 2010.⁹² As a result, BMS has

taken a decision to close its manufacturing plant in Meymac, France, in June 2010 which might affect the availability of some antiretrovirals for the developing world until the new production plant in the U.S. is able to produce those formulations again. In 2006, BMS discontinued the sale of the chewable / dispersible buffered tablets in the U.S. The enteric-coated capsules are more adaptable as they can be taken once daily and, unlike the tablets, do not contain a buffer. The buffer has been associated with stomach upsets and a bitter and chalky taste.

In December 2009, BMS discontinued the sale and manufacturing of ddl 200mg tablet globally due to low demand for the product.

Today, four generic ddl EC formulations are included in the WHO List of Prequalified Medicinal Products.

Patents

The patent on enteric-coated capsules was granted in Brazil, China, and ARIPO and OAPI countries. No application claiming a patent on enteric-coated

capsules has been published in India, allowing a generic version to be launched. However, where the patent has been granted in other developing countries, the importation of the more affordable version from India is blocked.

Paediatrics

For younger children, the only options are buffered tablets that come with a high pill burden, or the ddl powder for reconstitution, which requires multiple dilutions, first with water and then with an antacid, to obtain the final concentration. Once reconstituted, the solution must be refrigerated and must be discarded after 30 days.

BMS offers no differential price for the ddl EC 125mg, which is the best-adapted option for older children who can swallow.

Due to the imminent closure of the BMS facility in Meymac, France, in June 2010, a serious supply problem for didanosine 25mg and 50mg tablets of which there is no WHO prequalified generic source, is likely to emerge.

EMTRICITABINE (FTC)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults and adolescents.⁸
- Originator company and product brand name: Gilead, Emtriva.
- First approval by U.S. Food and Drug Administration (FDA): July 2003.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 28 million; 2008: \$31 million; 2007: \$32 million; 2006: \$36 million; 2005: \$47 million; 2004: \$58 million.^{93,94,95,96}
- The basic patent on FTC and lamivudine (3TC) was filed by IAF Biochem in 1990 and is due to expire in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.^{97,98}
- Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.^{99,100} These are due to expire between 2010 and 2012. In 2005, Gilead acquired the royalty interest for FTC under a \$525 million agreement with Emory University.¹⁰¹

PRICE INFORMATION

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

The price in brackets corresponds to the price of one capsule. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	Aurobindo	Matrix
Who can access this price?		No restrictions	
FTC 200mg capsule	1	63 (0.173)	79 (0.217)

SPOTLIGHT ON ACCESS ISSUES

Emtricitabine (FTC) produced by Gilead is not offered as part of the company's Access Program and is also neither registered nor marketed in developing countries. It is, however, available in co-formulation with tenofovir (TDF) and efavirenz (EFV).

According to the WHO treatment guidelines, 'FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.'⁸

The new WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.⁹

Patents

Although basic patents on FTC could not be applied for in India because the country did not grant patents on pharmaceuticals at the time, Gilead reported holding patent rights on FTC in 45 other developing countries.¹⁰²

In mid 2006, Gilead signed licensing agreements with 10 generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's TDF in combination with other ARVs – including FTC – to a limited list of countries, in return for the payment of a 5% royalty.¹⁰³

Paediatrics

FTC is approved for use in children and has the advantage of once-daily dosing.

The paediatric formulation produced by Gilead is a solution that requires refrigeration prior to dispensing and must be used within three months and stored at temperatures below 25°C. This is not adapted to developing world needs.



LAMIVUDINE (3TC)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults, adolescents and children.^{8,137}
- Originator company and product brand name: GlaxoSmithKline (GSK), Epivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 1995.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 197 million; 2008: \$225 million; 2007: \$309 million; 2006: \$398 million; 2005: \$398 million; 2004: \$549 million.^{104, 80, 81, 82}
- The basic patent on emtricitabine (FTC) and 3TC was filed by IAF Biochem in 1990 and is due to expire in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.⁹⁷
- GSK obtained a license from IAF to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which are due to expire around 2012.¹⁰⁵
- GSK also applied for a new formulation patent in 1998. This patent was granted in Brazil, China and in ARIPO countries.¹⁰⁶

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet/dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

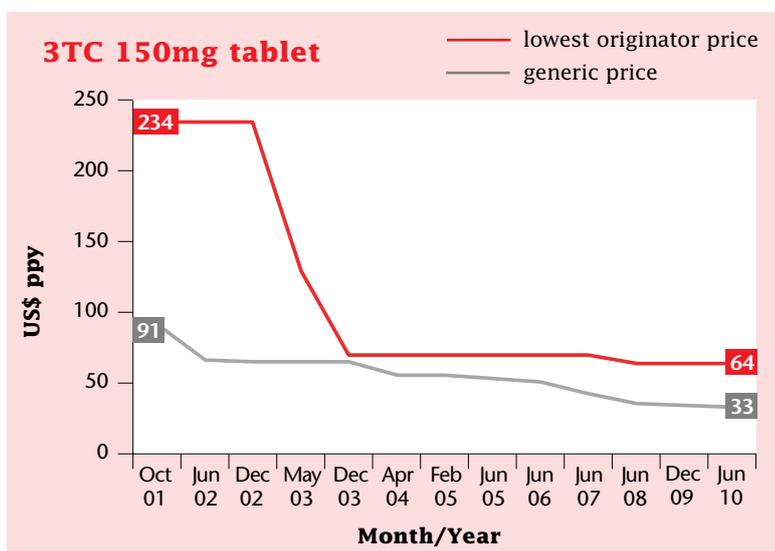
	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix	Ranbaxy (CF)	Strides
Who can access this price?		See annex 2	No restrictions					
3TC 10mg/ml oral solution	10ml	84 (0.023/ml)	29 (0.008/ml)	37 (0.010/ml)	37 (0.010/ml)			
3TC 150mg tablet	2	64 (0.087)	34 (0.047)	35 (0.048)	33 (0.045)	34 (0.046)	34 (0.047)	37 (0.050)
3TC 300mg tablet	1		24 (0.067)	41 (0.113)	38 (0.103)	34 (0.092)		

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

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

As of April 2010, there were nine generic sources of 3TC 150mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

The price of the originator product has fallen by 73% since 2001, while generic prices have dropped by 64%.



SPOTLIGHT ON ACCESS ISSUES

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

According to the WHO treatment guidelines, 'FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.'⁸

The new WHO 2010 guidelines recommend using TDF with either emtricitabine or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.⁹

Patents

As the graph illustrates, the price of 3TC decreased dramatically after the onset of generic competition. Generic competition for 3TC originated in countries with manufacturing capacity where the drug is not under patent, such as India, Thailand and Brazil.

In China, where GSK still owns exclusive rights on 3TC, the price of the medicine remains very high, at around US\$ 1,780 per patient per year. GSK is using its monopoly rights to block local production or importation of more affordable generic versions of 3TC.

Paediatrics

3TC is approved for use and is widely used in children.

Generic manufacturers have been developing both double and triple fixed-dose combinations containing 3TC. As of April 2010 there were four paediatric triple FDCs containing 3TC included in the WHO List of Prequalified Medicinal Products.

Today, once-daily dosing of 3TC is only recommended for patients over 16; more studies are needed to confirm the safety of daily dosing of 3TC in children.¹⁰



STAVUDINE (d4T)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first-line for children and also recommended to move away from d4T first-line in adults and adolescents.^{8,137}
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.¹⁰⁷
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- First approval by U.S. Food and Drug Administration (FDA): December 1994.¹⁷
- Included in the 16th edition WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2006: US\$ 155 million; 2005: \$216 million; 2004: \$272 million; 2003: \$354 million. After 2006, there are no sales figures listed in the company's annual report.^{108,49}
- d4T was the result of U.S. public sector research. It was originally synthesised by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.¹⁰⁹ Researchers from Yale University then discovered its antiretroviral activity and applied for a patent in December 1987, mostly in developed countries, for the use of d4T to treat patients infected with retroviruses.¹¹⁰ This patent should have expired in December 2007, but the protection was extended until the end of 2008 in the U.S. and until 2011 in most European countries. BMS markets d4T under a marketing and distribution licence from Yale University.
- Patents have expired in most other countries at this point.

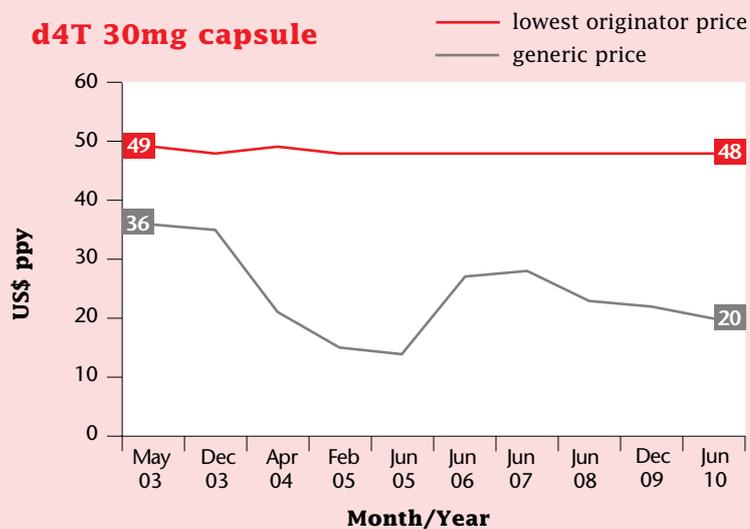
PRICE INFORMATION

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

The price in brackets corresponds to the price of one capsule/dose of powder for oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	BMS		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
		Category 1 countries	Category 2 countries						
Who can access this price?		See annex 2 & annex 7		No restrictions					
d4T 1mg/ml powder for oral solution	20 ml	51 (0.007/ml)	58 (0.008/ml)	58 (0.008/ml)	44 (0.006/ml)				
d4T 15mg capsule	-	(0.082)	(0.093)	(0.026)	(0.024)	(0.025)			
d4T 20mg capsule	-	(0.089)	(0.093)	(0.027)	(0.025)	(0.028)			
d4T 30mg capsule	2	48 (0.066)	68 (0.093)	20 (0.028)	26 (0.035)	21 (0.029)	24 (0.033)	26 (0.035)	22 (0.030)

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

d4T 30mg capsule**Evolution of the lowest price quoted for developing countries since 2003:**

As of April 2010, there were six generic sources of d4T 30mg capsule included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

Patents

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

In South Africa, where BMS marketed d4T under an exclusive license from Yale, the drug was 34 times more expensive than generic versions available in other countries. This prompted a patent 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 license with BMS to allow the importation of more affordable generic versions of d4T to South Africa.¹⁰⁹

Paediatrics

Stavudine is approved for use in children.

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

Generic manufacturers have been developing both double and triple fixed-dose combinations including d4T. For paediatric use, two d4t-containing triple FDCs are included in WHO List of Prequalified Medicinal Products.

TENOFOVIR DISOPROXIL FUMARATE (TDF)

GENERAL INFORMATION

- Therapeutic class: nucleotide reverse transcriptase inhibitor (NtRTI).
 - Indicated for first- and second-line for adults, adolescents and children.^{8, 137}
 - Originator company and product brand name: Gilead, Viread.
 - First approval by U.S. Food and Drug Administration (FDA): October 2001.¹⁷
 - Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
 - World sales of originator product: 2009: US\$ 667 million; 2008: \$621 million; 2007: \$613 million; 2006: \$689 million; 2005: \$778 million; 2004: \$783 million.^{93, 94, 111, 112, 95, 96}
 - 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.¹¹³
- Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997¹¹⁴ and to the fumarate salt of tenofovir disoproxil in 1998.¹¹⁵ These are due to expire in 2017 and 2018, respectively. In addition, Gilead and BMS have applied for patents on fixed-dose combinations of TDF/FTC and TDF/FTC/EFV which, if granted in developing countries, will not expire before 2024 and 2026 respectively.^{58, 59}

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

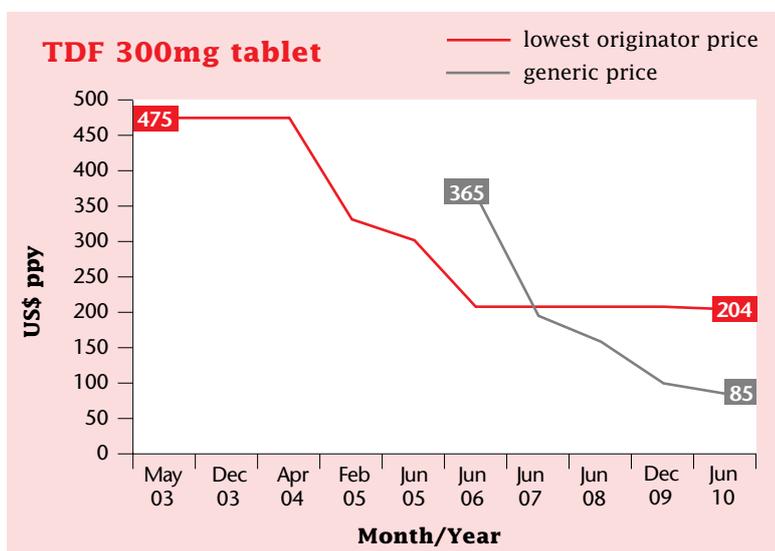
	Daily dose	Gilead		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
Who can access this price?		See annex 2 & annex 9			No restrictions				
TDF 300mg tablet	1	204 (0.559)	360 (0.986)	100 (0.275)	87 (0.237)	103 (0.283)	85 (0.233)	152 (0.417)	146 (0.400)

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

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

As of April 2010, there were four generic sources of TDF 300mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

There has been a 77% decrease in the generic price since 2006, and a 56% decrease in the lowest originator price since 2003.



SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.

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

It is time, however, for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill, once a day. While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.⁹

For second-line treatment, TDF in combination with lamivudine (3TC) or emtricitabine (FTC) are the recommended NRTI backbones to be added to a boosted protease inhibitor, if stavudine or zidovudine have been used in the first-line regimen.

TDF is also active against the Hepatitis B virus (HBV) and therefore plays an important role in co-infected patients. For HIV patients requiring treatment for HBV, the treatment should contain TDF and either 3TC or FTC.

Gilead has a differential pricing structure (see annex 9) that has been expanded to include lower-middle-income countries not included in its Access Program.

Patents

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

applications have been opposed by civil society groups, as well as by some generic manufacturers.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. 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. Further, combinations of known molecules are not patentable under Indian patent law.^{174, 175, 176}

Nevertheless, divisional applications (a type of patent application which contains matter from a previously filed application) have been filed by Gilead for this and other patent applications. This means that although the patent was not granted, the patent applications are still pending before the patent office.^{116, 117}

The same is true in Brazil, where an estimated 37,000 PLHA are on TDF-based therapies. In April 2008, the government declared tenofovir as a medicine of public interest for priority examination purposes. The National Institute on Industrial Property (INPI – Brazilian patent office) published the patent rejection for TDF on 30 June 2009. However, Gilead has requested a divisional patent, which has been opposed by civil society groups. In addition, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent.

Following oppositions (by members of Indian and Brazilian civil society) to the grant of its patents in India, Gilead signed licensing agreements with 11 generic manufacturers in India and one in South Africa, allowing them to manufacture and export generic versions of TDF and TDF-based FDCs to a limited pre-defined list of countries, against the payment of a 5% royalty.¹⁰³

Manufacturers that have signed these agreements are unable to supply

countries such as Brazil and China, leaving these countries unable to benefit from competitive prices and improve access. After negotiation with Gilead, Brazil is today paying US\$ 715 per patient per year for tenofovir, over eight times the best available generic price.¹²⁹ The Brazilian government is currently supporting the development of generic TDF through partnerships between Brazilian public and private manufactures.

Although the licensing agreements signed by Gilead can contribute to increased competition and improved access to affordable medicines, they should also be offered to manufacturers outside India, and should not include geographic market limitations.

Paediatrics

In March 2010, TDF was approved by the U.S. FDA for use in adolescents older than 12 years old and weighing more than 35kg.¹¹⁸

Gilead's Phase II trial involving children (aged between two and 12 years), using an oral powder formulation is still on-going. Such data, provided appropriate formulations are developed, will be crucial to address the urgent needs of this paediatric population.

In March 2009, U.S. FDA granted TDF an Orphan Drug designation for treatment of paediatric HIV infections.¹¹⁹ Gilead is now entitled to seven years of marketing exclusivity for the designated paediatric indication, tax credits for clinical research and can apply for grants to defray the cost of clinical trials.¹²⁰

ZIDOVUDINE (AZT or ZDV)

GENERAL INFORMATION

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults, adolescents and children.^{8,137}
- 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 approval by U.S. Food and Drug Administration (FDA): March 1987.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2005: US\$ 84 million; 2004: \$80 million. After 2005, there are no sales figures for this product listed in the company's annual report.^{78,79}
- AZT was first discovered in 1964 as an anti-cancer medicine. The U.S. National Institutes of Health did the majority of the research that showed the drug's effectiveness as an antiretroviral. Glaxo Wellcome filed for patents on AZT for the treatment of AIDS and brought the drug onto the market in 1987 as one of the most expensive ever sold. Patents have expired in most countries at this point.

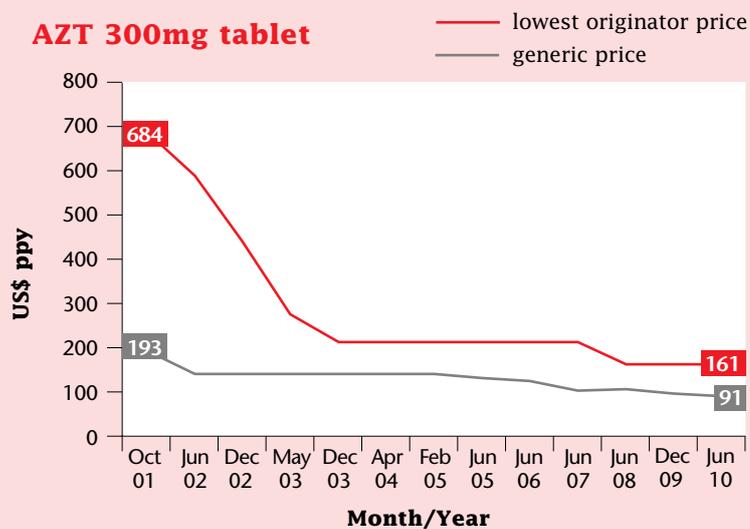
PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet/capsule/dose of suspension. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)
Who can access this price?		See annex 2	No restrictions				
AZT 10mg/ml suspension	20 ml	234 (0.032/ml)	66 (0.009/ml)	80 (0.011/ml)	66 (0.009/ml)		
AZT 60mg tablet	4		115 (0.079)				
AZT 100mg capsule	-	(0.122)	(0.051)	(0.050)			
AZT 250mg capsule	-	(0.276)					
AZT 300mg tablet	2	161 (0.221)	101 (0.138)	97 (0.133)	100 (0.137)	91 (0.125)	91 (0.125)

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

AZT 300mg tablet**Evolution of the lowest price quoted for developing countries since 2001:**

As of April 2010, there were seven generic sources of AZT 300mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 76%, while the generic price has decreased by 53%.

SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term

irreversible side effects and to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

For second-line treatment, and if tenofovir has been used in the first-line, AZT in combination with lamivudine (3TC) is the recommended NRTI backbone, to which a boosted protease inhibitor (PI) should be added.

Patents

Patents have expired in most countries at this point.

Paediatrics

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

Generic manufacturers have been developing both double and triple paediatric fixed-dose combinations including AZT. Today, however, there are four paediatric FDCs containing AZT that are included in WHO List of Prequalified Medicinal Products.

Today there is one generic version of AZT 60mg which is prequalified by WHO.

ATAZANAVIR (ATV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Boosted ATV is indicated for second-line for adults and adolescents.⁸
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approval by U.S. Food and Drug Administration (FDA): June 2003.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 1.4 billion; 2008: \$1.3 billion; 2007: \$1.1 billion; 2006: \$931 million; 2005: \$696 million; 2004: \$369 million; 2003: \$81 million.^{121, 50, 122, 108, 123}
- The basic patent was filed in April 1997 by Novartis and is expected to expire in April 2017.¹²⁴ Bristol-Myers Squibb is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998¹²⁵ and on a process for preparing the bisulfate salt and novel forms in 2005.¹²⁶

PRICE INFORMATION

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

The price in brackets corresponds to the price of one capsule. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	BMS		Matrix (CF)
		Category 1 countries	Category 2 countries	
Who can access this price?		See annex 2 & annex 7		No restrictions
ATV 150mg capsule	2*	353 (0.484)	431 (0.590)	
ATV 200mg capsule	-	(0.602)	(0.743)	
ATV 300mg capsule	1*			256 (0.700)

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

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

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).⁹ With its once-a-day dosing ATV is the most patient-friendly PI of the two.

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

The required addition of RTV as a booster must also be considered in the final cost of using ATV.

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

Patents

Patent applications related to ATV have been filed by Novartis and BMS in most developing countries with generic pharmaceutical production capacity, including Brazil, China

and India. Most patents have been granted in Brazil and China. In India, where the patent applications are still under examination, civil society organisations filed a pre-grant opposition to Novartis's basic patent application on the grounds of lack of novelty,¹²⁷ but the other patent applications warrant additional pre-grant oppositions.

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

BMS in February 2006 granted technology transfer and voluntary licences to two generic manufacturers (Emcure and Aspen) to manufacture and sell ATV. In February 2008, Emcure received U.S. FDA tentative approval for the 100mg, 150mg and 200mg ATV capsules. Under the terms of the licenses, 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.¹²⁸

Licensing agreements in India should not be necessary if patent oppositions are successful. If patents are granted, India and other countries could issue compulsory licences to enable unrestricted competition from

generic manufacturers, in order to bring prices down, increase access and facilitate the development of an ATV/r fixed-dose combination.

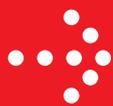
BMS's differential pricing structure is limited to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries such as Brazil paying more than US\$ 1,400 per patient per year, which is prohibitive for many of these countries.¹²⁹

Paediatrics

In March 2008, ATV was approved for use in children between 6 and 18 years of age.¹⁷

In 2008, WHO recommended early treatment for all HIV-positive children, and children who have been exposed to nevirapine either through their mother or through a single dose in a prevention of mother-to-child transmission (PMTCT) programme. WHO recommends these children should be started on a PI-based regimen.¹³⁰ Today, the only option for these children is the LPV/r formulation.

To simplify treatment for all children, there is an urgent need for studies on ATV to be completed down to infants, and child-adapted formulations to be made available.



DARUNAVIR (DRV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Boosted DVR is listed in WHO guideline as a potential third-line drug.⁸
- Indicated for treatment-experienced patients, such as those with HIV-1 strains resistant to more than one protease inhibitor (adults). It is also indicated in developed countries for treatment-naïve patients.¹³¹
- Originator company and product brand name: Tibotec (a division of Johnson&Johnson), Prezista.
- First approved by the U.S. Food and Drug Administration (FDA): June 2006.¹⁷
- World sales of originator product: there are no sales figures listed in the company's annual report.
- Not included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- The basic patent was applied for by Searle and Monsanto in August 1993,¹³² and is due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to darunavir in 1999¹³³ and licensed them to Tibotec for development.¹³⁴ Tibotec later applied for patents related to improved forms and combinations of darunavir.

PRICE INFORMATION

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

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

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

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

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations which for the first time call for the need of third-line therapy. As many studies are ongoing, drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.⁹

Tibotec signed a royalty-free, non-exclusive license agreement with Aspen of South Africa on 4 April 2007. This grants Aspen the right to register, package and distribute darunavir (DRV) in sub-Saharan Africa. In December 2008, Tibotec announced the signing of a royalty-free, non-exclusive license agreement with Emcure to distribute DRV in India.¹³⁶ These agreements exclude other low- and middle-income countries, for which the price paid in wealthy countries, at over US\$ 11,400 per patient per year, is prohibitive.³⁷

More recently, Tibotec completed a supply and co-marketing agreement with Aspen Pharmacare covering all of Africa. Under this agreement, Aspen will handle regulatory, registration, and distribution activities. At the time of writing, the Aspen/Tibotec product is registered in at least eight countries with applications in process in 11 others, primarily for the 400mg product but also for 300mg and paediatric formulations. Patient numbers in Africa for DRV are still small, and Aspen has agreed to a \$1,095 per patient per year for 300mg and 400mg formulations.

In Brazil, DRV was included in the government's guidelines in 2008,

but at \$6,037 per patient per year (boosted with ritonavir), it is very expensive.¹²⁹

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

The required addition of RTV as a booster must also be considered in the final cost of using DRV.

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

Patents

Even though basic patents related to DRV could not be applied for in India before 1995, Tibotec has applied for several patents in India related to new forms and combinations of DRV with tenofovir (TDF) and ritonavir (RTV), some of which have been opposed by generic manufacturers. Most of these patent applications remain under review at the Indian patent office. The Indian patent office recently rejected the DRV patent related to pseudopolymorph (which would have been due to expire in 2023). A voluntary license for the DRV pseudopolymorph has been granted in South Africa.

In China, patents related to racemic and pseudopolymorphic forms of DRV, methods for preparing

intermediate compounds of DRV and use of DRV in combination with other ARVs, have been granted to Tibotec.³⁹

Similarly, many patents 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 pseudopolymorphic form.

Paediatrics

In December 2008, DRV was approved for use in children between six and 18 years of age.¹⁷

A paediatric 75mg tablet is available, but Tibotec has not provided price information for this product. It is however, available on a compassionate use basis (free of charge) for sub-Saharan Africa and least-developed countries, until a pre-approval access programme is established with a local partner.

The Paediatric Antiretroviral Working Group of WHO considers the development of a fixed-dose combination containing darunavir and ritonavir to be a high priority, though it is still unclear what the ratio of the co-formulation will be.¹³⁷

FOSAMPRENAVIR (FPV or f-APV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Not currently included in WHO guidelines.
- Originator company and product brand name: GlaxoSmithKline (GSK) and Vertex Pharmaceuticals, Lexiva. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approved by the U.S. Food and Drug Administration (FDA) on: October 2003.¹⁷
- Not included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: there are no sales figures listed in the company's annual report.
- The basic patent was applied for by Vertex Pharmaceuticals in March 1998,¹³⁸ and due to expire in 2018. Fosamprenavir, a phosphate ester prodrug of amprenavir,¹³⁹ was developed and launched by GSK, under license from Vertex. GSK also holds patents related to a crystalline form of the calcium salt of FPV,¹⁴⁰ due to expire in 2019.

PRICE INFORMATION

	Daily dose	ViiV
Who can access this price?		See annex 2
FPV 50mg/ml suspension	12 ml*	648 (0.148/ml)
FPV 700mg tablet	2*	1222 (1.674)

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

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

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

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).⁹ As fosamprenavir (FPV) was not identified as one of the priority products, its use will be limited in the developing world.⁹

While FPV/r based regimens show good antiviral efficacy and are generally well tolerated in therapy-naïve patients, the experience of this drug in developed countries is limited and little comparative data is available in treatment-experienced patients.¹⁴¹

FPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV).

Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir.

The required addition of RTV as a booster must also be considered in the final cost of using FPV.

Patents

Patent applications have been filed for in many developing countries. In Brazil the basic patent was rejected by the patent office, although in December 2009 the company filed an appeal against the decision.

In China, South Africa, ARIPO and OAPI countries,¹⁴² most patents have been granted.

In India, patent applications on the FPV salts, including calcium, have been filed and are pending review by the patent office.

There are no generic formulations of this product available today.

Paediatrics

FPV was approved for use in children above the age of two in October 2007¹⁷ and a paediatric suspension is available.

INDINAVIR (IDV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Not currently included in WHO guidelines.
- Originator company and product brand name: Merck, Crixivan.
- First approval by U.S. Food and Drug Administration (FDA): March 1996.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: there are no sales figures listed in the company's annual report.
- The basic patent was filed for by Merck in 1991 and is due to expire in 2012 in countries granting 20-year patents.¹⁴³

PRICE INFORMATION

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

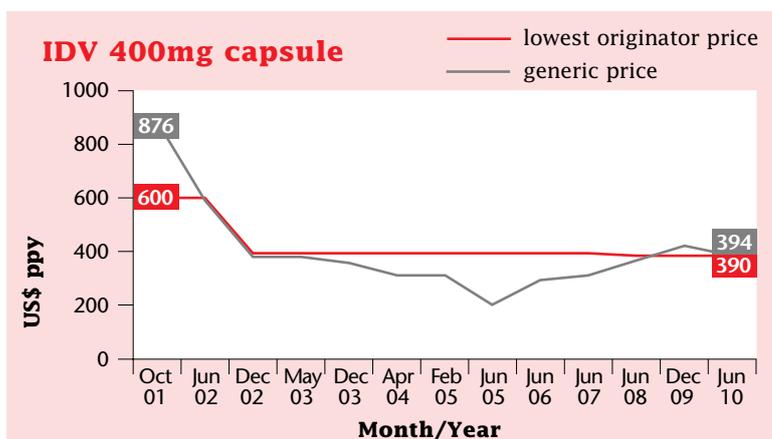
The price in brackets corresponds to the price of one capsule. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	Merck		Aurobindo	Cipla	Hetero
		Category 1 countries	Category 2 countries			
Who can access this price?		See annex 2 & annex 10		No restrictions		
IDV 400mg capsule	4*	394 (0.270)	686 (0.470)	292 (0.200)	422 (0.289)	390 (0.267)

* 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 April 2010, there were two generic sources of IDV 400mg capsule included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.



SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As IDV was not identified as one of the priority products, its use will be limited in the developing world.⁹

The main concern was that at a standard dose of 800mg with 100mg ritonavir (RTV) twice a day, IDV is less well tolerated than other PIs, particularly in hot climates.¹⁴¹ There have been some small studies to

support a lower dose of IDV + RTV 400 + 100mg twice a day with the aim to reduce toxicity. The U.S. FDA has also approved the use of IDV at 800mg every eight hours without RTV.

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

The required addition of RTV as a booster must also be considered in the final cost of using IDV.

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

Patents

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

Paediatrics

The optimal dosing regimen for the use of IDV in paediatric patients has not been established and no paediatric formulation exists.¹⁴⁴

LOPINAVIR/ RITONAVIR (LPV/r)

GENERAL INFORMATION

- Therapeutic class: boosted Protease Inhibitor (PI) in a double fixed-dose combination.
- Indicated for second-line, for adults, adolescents and children.^{8, 137}
- First approval by U.S. Food and Drug Administration (FDA): September 2000 (soft-gel capsules); October 2005 (heat-stable tablets).¹⁷
- Originator company and product brand name: Abbott Laboratories, Kaletra/Aluvia.
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2009: US\$ 1.366 billion; 2008: \$1.47 billion; 2007: \$1.32 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million.^{145, 146, 147}
- Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.¹⁴⁸
- In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997¹⁴⁹ which are due to expire in 2017. An application for a patent on the heat-stable tablet formulation was also filed in 2004,¹⁵⁰ which, if granted, would 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 price of one capsule /tablet/dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

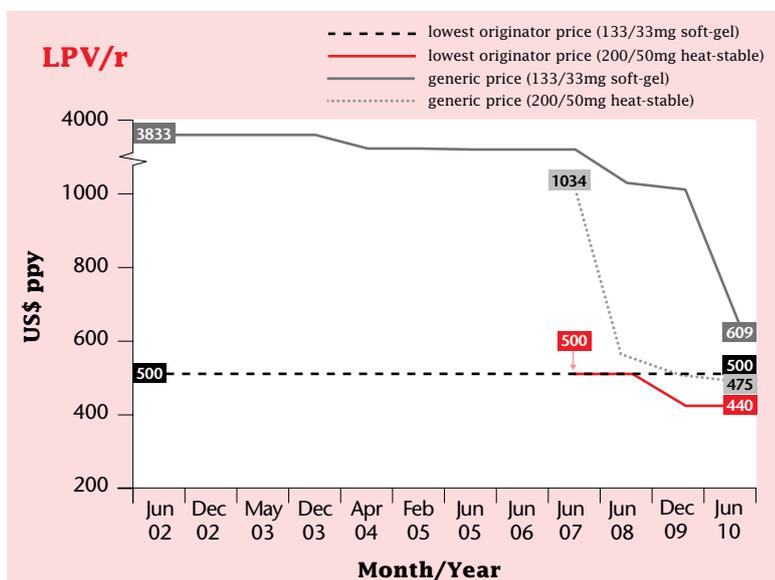
	Daily dose	Abbott		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 8		No restrictions			
LPV/r 80/20mg/ml oral solution	4 ml	176 (0.121/ml)	400 (0.274/ml)				
LPV/r 100/25mg heat-stable tablet	3	165 (0.151)	376 (0.343)	219 (0.200)			228 (0.208)
LPV/r 133/33mg soft-gel capsule	6	500 (0.228)	1000 (0.457)		609 (0.278)		
LPV/r 200/50mg heat-stable tablet	4	440 (0.301)	1000 (0.685)	475 (0.325)	463 (0.317)	493 (0.338)	486 (0.333)

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

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

As of April 2010, there was no generic source of LPV/r 133/33mg soft-gel capsule included in the WHO List of Prequalified Medicinal Products, so the lowest priced generic is considered in this graph. There were however two generic sources of LPV/r 200/50mg heat-stable tablet included in the list. The one with the lowest price is shown here.

The generic price of LPV/r 200/50mg heat-stable tablet has decreased by 54% since 2007.



SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).⁹

The heat-stable formulation of LPV/r manufactured by Abbott and Indian generic companies is now marketed in developing countries. In comparison to the older, soft-gel capsule formulation, the new formulation has a lower pill count (reducing the burden from six to four pills per day), there is no need for refrigeration, and there are no dietary restrictions. It is now approved as once-a-day dosing in treatment-experienced patients with fewer than three lopinavir resistance-associated mutations.¹⁷ This should enhance adherence. However, pill burden remains an issue.

The entry of generic manufacturers is having a positive effect on the market, and prices are declining. The Clinton Foundation's most recent announcement has some generic manufacturers offering prices of US\$ 440 per patient per year (see annex 13 for details).

Patents

In India, Abbott has applied for several patents on the solid dosage formulation and polymorphic forms of lopinavir (LPV), ritonavir (RTV) and on the heat-stable combination of LPV/r, a number of which have been opposed by civil society organisations¹⁵¹ and generic companies. Following a pre-grant opposition to the application related to the soft-gel formulation of LPV/r, the application was withdrawn by the company. Other oppositions are pending decisions by the Indian patent office.

If one of these patent applications is granted, current generic competition, which is bringing prices substantially down as demand increases, will be under threat.

India and other countries could issue compulsory licences to enable unrestricted competition from generic manufacturers to continue.

In Thailand, where Abbott holds patents, the price of LPV/r was US\$ 2,200 ppy in 2007. In January 2007, the Ministry of Public Health issued a compulsory licence to import more affordable generic versions of the drug from India.⁵³ Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies and Abbott's response was to withdraw all registration applications in Thailand for its new products, including the heat-stable LPV/r. Thailand today imports generic LPV/r from India for \$793 ppy.⁵⁴

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 \$1,380.¹⁵²

Indeed, the basic patent for LPV/r is protected in Brazil under the so-called 'pipeline mechanism', a provision in Brazilian patent law deemed to be in excess of the minimum standards for intellectual property protection under the TRIPS Agreement.

In 2007, the National Federation of Pharmacists (Fenafar) – on behalf of the Brazilian Network for the Integration of Peoples (Rebrip) - requested the Brazilian Prosecutor General consider overturning the pipeline mechanism as unconstitutional. They argue that these patents should not be granted in Brazil on the basis that they had not gone through the regular analysis process for patent applications and that they go against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court. MSF-Brazil is actively following the case.¹⁵³

Paediatrics

LPV/r is approved for use in children from two weeks old.¹⁷

In early 2007, Abbott released a paediatric LPV/r 100/25mg heat-stable tablet. While this new formulation is welcome, it does not help the youngest patients, as the tablet is 15mm long and cannot be crushed, leaving this formulation unsuitable for children who cannot swallow tablets.

The alternative for these small children is a solution that requires refrigeration until dispensing, after which it must be stored below 25°C for no more than six weeks. Furthermore, the solution consists of 42% alcohol and has a very unpleasant taste.

There is an urgent need for more adapted heat-stable paediatric formulation of LPV/r (such as soluble granules or sprinkles) for young children who can not swallow the existing tablet. A heat-stable sprinkle in a paediatric dose is under development by generic companies. The Paediatric Antiretroviral Working Group of WHO considers the development of a LPV/r 40/10mg heat-stable sprinkle to be a high priority.¹³⁷

Today there are two generic sources of heat-stable LPV/r 100/25mg included in the WHO List of Prequalified Medicinal Products.

Recent changes in the WHO guidelines recommending that all HIV-positive children under one year of age start ARV therapy as soon as possible regardless of clinical status, combined with the recommendation to start all children exposed to nevirapine on a PI-based regimen, should result in an increased demand for this combination for very young children.¹³⁰

NELFINAVIR (NFV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Deleted from the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2004: US\$ 259 million. After 2004, there are no sales figures listed in the company's annual report.¹⁵⁴
- The basic patent was applied for in 1994 by Agouron Pharmaceuticals Inc.,¹⁵⁵ and is due to expire in 2014. Agouron Pharmaceuticals is now a subsidiary of Pfizer. NFV was developed by Agouron as part of a joint venture with Japan Tobacco, Inc. NFV is supplied by Roche outside the U.S., Canada and Japan.¹⁵⁶
- Not currently included in WHO guidelines.
- Originator company and product brand name: Roche, Viracept.
- First approval by U.S. Food and Drug Administration (FDA): March 1997.¹⁷

PRICE INFORMATION

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

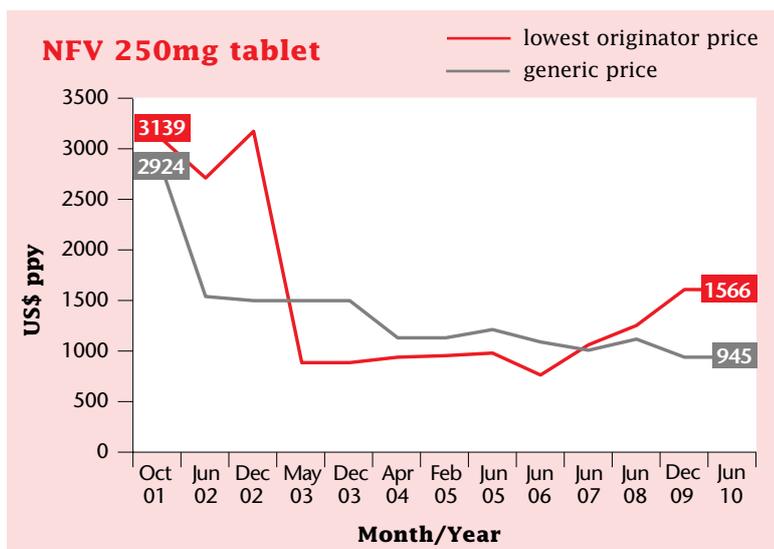
The price in brackets corresponds to the price of one tablet/gram. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	Roche		Cipla
		Category 1 countries	Category 2 countries	
Who can access this price?		See annex 2		No restrictions
NFV 50mg/g oral powder	24g	2129 (0.243/g)	2462 (0.281/g)	
NFV 250mg tablet	10	1566 (0.429)	2427 (0.665)	945 (0.259)

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

As of April 2010, there was no generic source of NFV 250mg tablet included in the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown here.

Roche quotes prices in Swiss Francs (CHF), which were converted to US\$ on the date received. Fluctuations in the US\$/CHF rate will thus have an impact on prices used in the graph.



SPOTLIGHT ON ACCESS ISSUES

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

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

In June 2007, Roche recalled all batches of NFV due to high levels of Ethyl Methane Sulphonate (EMS), a by-product of the manufacturing process and a known carcinogen in animals. Roche's marketing licence for NFV was suspended in Europe and the WHO prequalification project temporarily suspended the product. In September 2007, the suspensions were lifted and marketing licences reinstated.¹⁵⁷

As a result of the recall, many patients were changed to another PI. It is unknown if there will continue to be demand for the NFV formulation in the future. NFV was also deleted from the 16th edition of the WHO Model List of Essential Medicines (EML).

Patents

Even though patents could not be applied for in India prior to 1995, Agouron applied for patents on NFV in many other developing countries. This factor contributes to the high price of the drug, together with the small demand.

The recall of Roche's NFV in 2007 highlights the risk associated with relying on a single producer for a medicine.

Paediatrics

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

Not only is the paediatric NFV formulation ill-adapted, but its price remains prohibitive, as is the case with other protease inhibitors.

RITONAVIR (r or RTV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line as a booster, for adults, adolescents and children.^{8,137}
- Originator company and product brand name: Abbott Laboratories, Norvir.
- First approval by U.S. Food and Drug Administration (FDA): March 1996 for the oral solution and June 1999 for capsules.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: 2004: US\$ 194 million; 2003: \$93 million; and 2002: \$122 million.¹⁵⁸ After 2004, there are no sales figures listed in the company's annual report.
- The basic patent was applied for by Abbott in 1993.¹⁵⁹ Subsequently, Abbott applied for patents related to polymorphic forms of RTV^{149,160} and to a soft-gel capsule formulation.¹⁶¹ These are due to expire respectively in 2019 and 2020.

PRICE INFORMATION

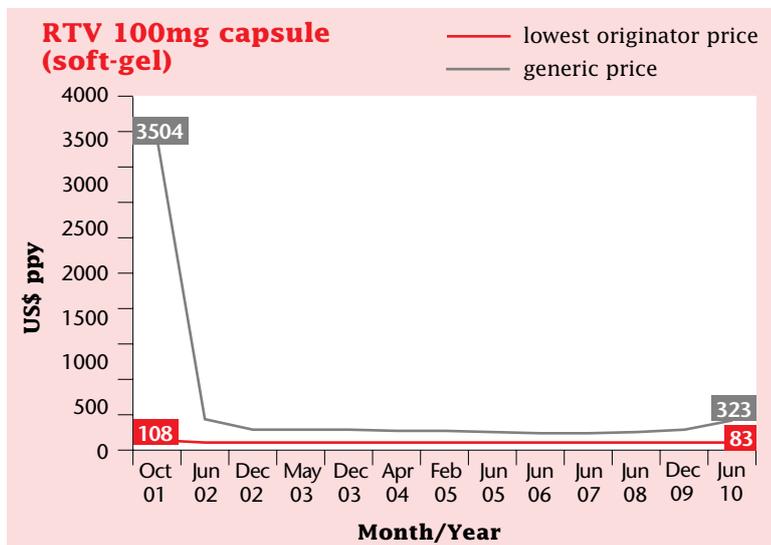
Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule / tablet / dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose, used as booster	Abbott	Cipla
Who can access this price?		See annex 2 & annex 8	No restrictions
RTV 80mg/ml oral solution	-	(0.093/ml)	
RTV 100mg soft-gel capsule	2	83 (0.114)	323 (0.442)
RTV 100mg heat-stable tablet	2	83 (0.114)	

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

As of April 2010, there was no generic source of RTV 100mg soft-gel capsule included in the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown here.



SPOTLIGHT ON ACCESS ISSUES

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

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

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

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

Patents

Although the basic patent disclosing RTV could not be applied for in India, Abbott's original patent applications and divisional applications on new forms of RTV are pending before the Indian patent office. A pre-grant opposition to an application related to a polymorph of RTV was filed by civil society organisations in India in September 2006.¹⁵¹ The decision of the Indian patent office is pending. The outcome of this opposition will be crucial to the management of PI-based second-line treatment.

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

On 14 April 2010, Ecuador issued its first compulsory licence allowing Eskegroup SA, the local distributor for Cipla, to manufacture, offer for sale, sell, use or import RTV, or compositions including RTV, for public non-commercial use, against the payment of royalties to Abbott, until the patent expiration date in 2014.¹⁶²

The compulsory licence followed a decree of Ecuadorian President Rafael Correa in October 2009, declaring access to essential medicines of public interest to the Ecuadorean population and allowing the national intellectual property office to issue compulsory licences to this end, based on Article 31 of the TRIPS Agreement.¹⁶³

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

Paediatrics

RTV is approved for use in children and there is a liquid formulation available. The solution has a bitter aftertaste and is 43% alcohol, and hence not adapted for children.

The Paediatric Antiretroviral Working Group of WHO considers the development of a RTV 50mg heat-stable sprinkle or tablet to be a high priority.¹³⁷



SAQUINAVIR (SQV)

GENERAL INFORMATION

- Therapeutic class: protease inhibitor (PI).
- Not currently included in WHO guidelines.
- Originator company and product brand name: Roche, Invirase.
- First approval by U.S. Food and Drug Administration (FDA): December 1995.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: there are no sales figures listed in the company's annual report.
- The basic patent was applied for by Roche in 1990¹⁶⁴ and is due to expire in December 2010 in countries not granting patent extensions.
- A patent related to oral dosage form was applied by Roche in 2004 and is due to expire in 2024.¹⁶⁵

PRICE INFORMATION

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

The price in brackets corresponds to the price of one capsule / tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

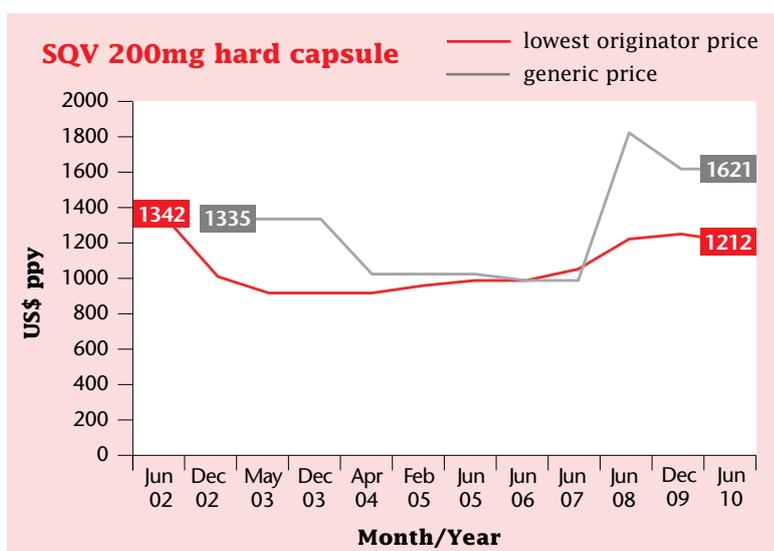
	Daily dose	Roche		Cipla
		Category 1 countries	Category 2 countries	
Who can access this price?		See annex 2		No restrictions
SQV 200mg hard capsule	10*	1212 (0.332)	2427 (0.665)	1621 (0.444)
SQV 500mg tablet	4*	1113 (0.762)	2427 (1.662)	

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

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

As of April 2010, there was no generic source of SQV 200mg hard capsule included in the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown here.

Roche quotes prices in Swiss Francs (CHF), which have been converted to US\$ on the date received. Fluctuations in the US\$/CHF rate will thus have an impact on prices used in the graph.



SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As saquinavir (SQV) was not identified as one of the priority products, its use in the developing world will be limited.⁹

SQV/r appears to be slightly less potent than the other boosted PIs and in the original formulation has a high pill count (10 capsules).¹⁴¹ In 2004, Roche marketed a 500mg tablet of SQV in the U.S. that reduced the pill count from 10 tablets to four. While this new formulation should improve adherence, it is only registered and marketed in selected developing countries.

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

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

The required addition of RTV as a booster must also be considered in the final cost of using SQV.

Patents

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

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

Paediatrics

SQV has not been approved for use in children in the U.S. and there is no paediatric formulation available.

TIPRANAVIR (TPV)

GENERAL INFORMATION

- Therapeutic class: Protease Inhibitor (PI).
- Not currently included in WHO guidelines.
- TPV is indicated for combination treatment of HIV-1 infected adult patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.¹⁶⁶
- Originator company and product brand name: Boehringer Ingelheim (BI) Pharmaceuticals, Aptivus.
- First approved by the U.S. Food and Drug Administration (FDA): June 2005.¹⁷
- Not included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- World sales of originator product: there are no sales figures listed in the company's annual report.
- The basic patent was applied for by Upjohn in May 1995,¹⁶⁷ and is due to expire in 2015. In 1998, Pharmacia & Upjohn applied for additional patents related to pharmaceutical formulations suitable for the oral administration of TPV.^{168, 169} In January 2000, BI acquired worldwide rights for TPV.

PRICE INFORMATION

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

SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As tipranavir (TPV) was not identified as one of the priority products, its use in the developing world will be limited.⁹

Boehringer Ingelheim was invited to contribute a price for this publication and has communicated that tipranavir (TPV) is available through its Compassionate Use Program and that the company is currently filing for registration in various countries.

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

Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir.

The required addition of RTV as a booster must also be considered in the final cost of using TPV.

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

Patents

TPV patents have been filed for widely in developing countries with generic production capacity, such as Brazil and China.³⁹

In Brazil, where the patent applications are under review, the drug regulatory agency (ANVISA), which has to give 'prior consent' for any patent application related to a medicine, has advised for the rejection of the basic patent application.¹⁷⁰

In early 2007, civil society expressed concerns over the delays to the registration procedure of TPV in Brazil (the medicine had been tested in Brazilian patients in 14 research centres since February 2004, but the drug was not actually registered in the country). After considerable civil society pressure, the registration was eventually filed with ANVISA at the end of February 2008, almost three years after U.S. FDA and EMA approvals. The intervention by Brazilian civil society was partly based in response to suspicions that Boehringer Ingelheim did not want to register the product in the country, unless they had the guarantee that the patent would be granted by the patent office.^{171, 172}

Paediatrics

TPV is currently approved for use in children from two years of age and older, and a paediatric oral solution exists.¹⁷

ABACAVIR/ LAMIVUDINE (ABC/3TC)

GENERAL INFORMATION

- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first- and second-line for children and as part of triple NRTI drugs under specific conditions in adults, adolescents and children.^{8,137}
- Originator company, and product brand name: GlaxoSmithKline (GSK), Kivexa (EU), Epzicom (U.S.). In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.¹⁷
- 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.²⁶
- World sales of originator product: 2009: US\$ 834 million; 2008: \$721 million; 2007: \$641 million; 2006: \$475 million; 2005: \$233 million.^{77, 79, 80, 81, 82}
- Most patents on abacavir (ABC) or lamivudine (3TC) also affect this combination. In addition, GSK applied for patents more specifically related to the combination.¹⁷³ The patent expiry dates related to this combination are 2016 in the U.S. and 2019 in EU.⁸²

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

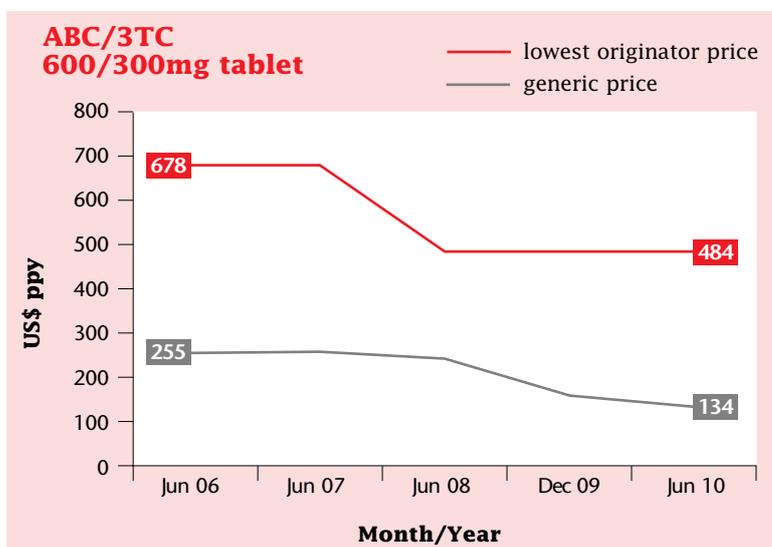
	Daily dose	ViiV	Aurobindo (CF)	Cipla	Matrix (CF)
Who can access this price?		See annex 2	No restrictions		
ABC/3TC 60/30mg tablet	4		175 (0.120)		244 (0.167)
ABC/3TC 600/300mg tablet	1	484 (1.326)	134 (0.367)	152 (0.417)	

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

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

As of April 2010, there was one generic source of ABC/3TC 600/300mg tablet included in the WHO List of Prequalified Medicinal Products. Its price is shown here.

There has been a decrease of 47% in the generic price since 2006.



Continued overleaf

❖ Abacavir/Lamivudine (ABC/3TC) continued

SPOTLIGHT ON ACCESS ISSUES

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

Patents

GlaxoSmithKline could not apply for basic patents related to abacavir (ABC) or lamivudine (3TC) in some developing countries such as India that did not grant patents on pharmaceutical products at the time. This allowed Indian drug manufacturers to develop generic versions of each medicine, and of the combination of the two.

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

Paediatrics

The Paediatric Antiretroviral Working Group of WHO considers the development of a scored adult fixed-dose combination of ABC/3TC 300/150mg tablet, for use in children weighing over 25kg, to be a high priority.¹³⁷

ViiV does not produce a fixed-dose combination of these drugs for children – even though the FDCs exist for adults. Nevertheless, for children who need this combination, there are two generic sources included in the WHO List of Prequalified Medicinal Products.

The Paediatric Antiretroviral Working Group of WHO also considers the development of a triple fixed-dose combination of abacavir/lamivudine/nevirapine 60/30/50mg tablet to be a high priority.¹³⁷

LAMIVUDINE/ STAVUDINE (3TC/d4T)

GENERAL INFORMATION

- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first-line in children and it is recommended to move away from d4T in first-line in adults and adolescents.^{8,137}
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.¹⁰⁷
- 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.²⁶
- Included in the 16th edition WHO Model List of Essential Medicines (EML) – only the d4T 30mg presentation.²⁶
- Individual patents on lamivudine (3TC) or stavudine (d4T) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of both medicines in combination, or to the FDC.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

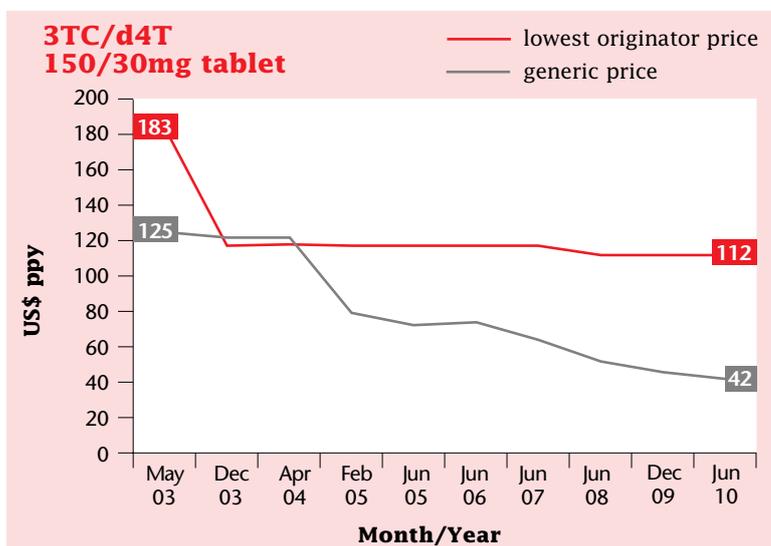
	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		No restrictions					
3TC/d4T 30/6mg dispersible tablet	4		47 (0.032)				
3TC/d4T 60/12mg dispersible tablet	2		40 (0.055)				
3TC/d4T 150/30mg tablet	2	50 (0.068)	42 (0.057)	51 (0.070)	42 (0.058)	42 (0.058)	44 (0.060)

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

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

As of April 2010, there were six generic sources of 3TC/d4T 150/30mg tablet included in the WHO List of Prequalified Medicinal Products. The one with 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.

There has been a 39% decrease in the originator price and a 66% decrease in generic price since 2003.



Continued overleaf ❖

❖ *Lamivudine/Stavudine (3TC/d4T) continued*

SPOTLIGHT ON ACCESS ISSUES

This combination has been an important formulation that has fostered treatment scale-up in resource-limited settings.

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

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

Patents

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

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

Paediatrics

The most commonly used first-line regimens for children today are either 3TC+d4T+NVP or AZT+3TC+NVP. With both of these regimens, there is a need to start nevirapine (NVP) at a lower dose for the first two weeks to minimise the side effects.

For children who need this double 3TC/d4T fixed-dose combination, there are two generic products included in the WHO List of Prequalified Medicinal Products.

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

GENERAL INFORMATION

- Therapeutic class: triple fixed-dose combination of two NRTIs and a NNRTI.
- Indicated for first-line for children and it is recommended to move away from d4T-based first-line in adults and adolescents.^{8,137}
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.¹⁰⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML) – only the d4T 30mg presentation.²⁶
- 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.²⁶
- Individual patents on lamivudine (3TC), stavudine (d4T) or nevirapine (NVP) also affect this combination. In addition, other patents may have been applied for more specifically relating to the use of the medicines in combination or to the fixed-dose combination. Cipla first developed the FDC and applied for patents in several African countries.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

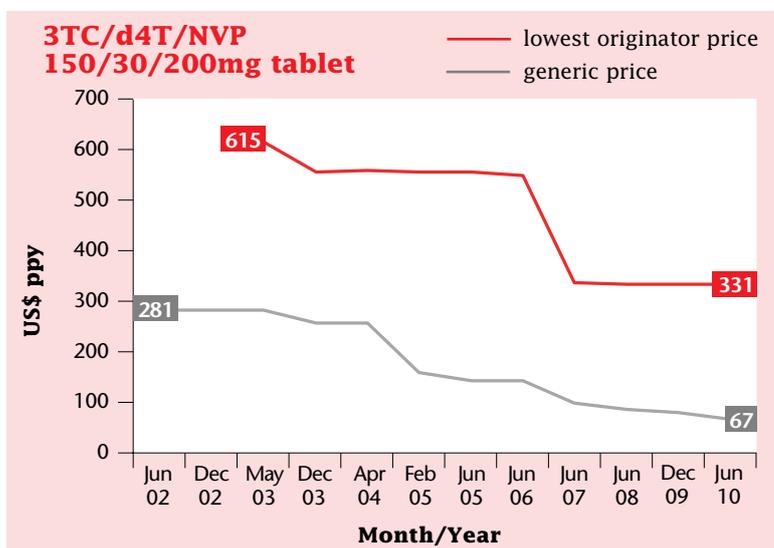
	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		No restrictions					
3TC/d4T/NVP 30/6/50mg dispersible tablet	4		55 (0.038)				
3TC/d4T/NVP 60/12/100mg dispersible tablet	2		53 (0.072)				
3TC/d4T/NVP 150/30/200mg tablet	2	67 (0.092)	67 (0.092)	73 (0.100)	67 (0.092)	70 (0.096)	73 (0.100)

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

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

As of April 2010, there were nine generic sources of 3TC/d4T/NVP 150/30/200mg tablet included in the WHO List of Prequalified Medicinal Products. The one with 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.

There has been a decrease of 76% in the generic price since 2002.



Continued overleaf

❖ *Lamivudine/Stavudine/Nevirapine (3TC/d4T/NVP) continued*

SPOTLIGHT ON ACCESS ISSUES

This combination is likely to fall out of favour since the latest WHO adults and adolescents guidelines recommended an AZT- or TDF-based first-line regime.

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and develop a plan to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

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

Patents

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

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

Paediatrics

This is one of the most-commonly used first-line regimens for children today.

The Paediatric Working Group at WHO has released clear guidance on the ideal strength of each of the individual ARVs in these fixed-dose combinations, and today there are two formulations included on WHO List of Prequalified Medicinal Products.¹⁰

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

GENERAL INFORMATION

- Therapeutic class: two NRTIs + one NNRTI in a co-pack.
- Indicated for first-line for children and it is recommended to move away from d4T based first-line in adults and adolescents.^{8,137}
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.¹⁰⁷
- Included in the WHO Model List of Essential Medicines (EML) - only the d4T 30mg presentation.²⁶
- 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.²⁶
- Individual patents on lamivudine (3TC), stavudine (d4T) or efavirenz (EFV) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of the medicines in combination, or to the FDC.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one kit (3 tablets). Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

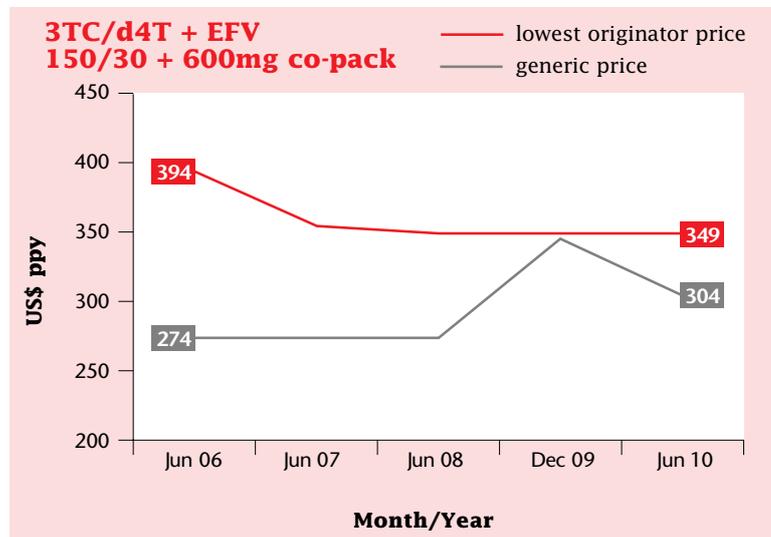
	Daily dose	Cipla (CF)	Ranbaxy	Strides (CF)
Who can access this price?		No restrictions		
3TC/d4T + EFV 150/30 + 600mg tablets (co-pack)	1 kit (3 tablets)	274 (0.751)	304 (0.833)	106 (0.290)

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

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

As of April 2010, there was one generic source of 3TC/d4T + EFV 150/30 + 600mg co-pack included in the WHO List of Prequalified Medicinal Products. Its price is shown here. As there is no originator co-pack, the price shown for the originator product is the sum of the three individual originator products.

The combined price of the originator products for 3TC/d4T + EFV 150/30 + 600mg has decreased by 11% since 2006. The generic co-pack included in the WHO List of Prequalified Medicines is a further 13% cheaper than the sum of originator products.



SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards

zidovudine (AZT) or tenofovir (TDF) - based first-line regimens.⁹

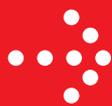
We can therefore expect to see a decrease in the use of this formulation in the future.

Patents

Generic companies in certain developing countries were

able to develop this co-blister because patents on the individual components contained in the combination did not exist.

This product is thus 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 + one NRTI in a double fixed-dose combination.
- Indicated for first-line and second-line for adults and adolescents.⁸
- Originator company and product brand name: Gilead, Truvada.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- World sales of originator product: 2009: US\$ 2.49 billion; 2008: \$2.11 billion; 2007: \$1.59 billion; 2006: \$1.19 billion; 2005: \$568 million; 2004: \$68 million.^{93,96}
- Most patents related to tenofovir (TDF) or to emtricitabine (FTC) also affect this combination. In addition, Gilead applied for patents specifically related to this combination in 2004, which are due to expire in 2024.⁵⁸

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

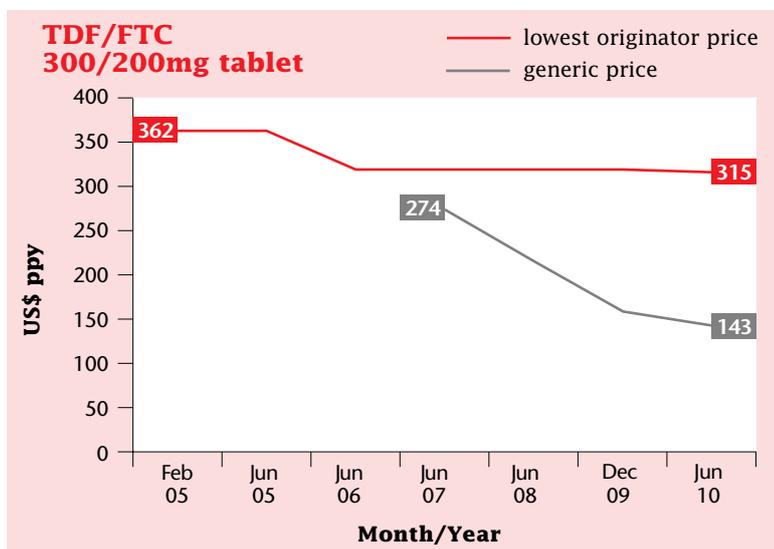
	Daily dose	Gilead		Aurobindo (CF)	Cipla	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 9		No restrictions			
TDF/FTC 300/200mg tablet	1	315 (0.863)	540 (1.479)	155 (0.425)	158 (0.433)	164 (0.450)	143 (0.392)

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

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

As of April 2010, there were two generic sources of TDF/FTC 300/200mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

Since 2007, there has been a 48% decrease in the generic price.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

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

It is however time for countries to invest in a more robust, TDF-based first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill once a day. While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.⁹

For second-line treatment, TDF in combination with lamivudine (3TC) or emtricitabine (FTC) are the recommended NRTI backbones, to be added to a boosted protease inhibitor, if stavudine or zidovudine have been used in the first-line regimen.

TDF is also active against Hepatitis B Virus (HBV) and therefore plays an important role in co-infected patients. For HIV patients also requiring treatment for Hepatitis B, the first- and second-line treatment should contain TDF and either 3TC or FTC.

Today, there are two generic sources of this combination included in the WHO List of Prequalified Medicinal Products.

Patents

This combination is produced by Indian generic companies because neither of the individual components is patented in India today. However, Gilead has applied for patents related to TDF. If these patents are granted in India, generic competition for this product may be affected.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. 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. Further, combinations of known molecules are not patentable under Indian patent law.^{174, 175, 176}

Nevertheless, divisional applications (a type of patent application which contains matter from a previously filed application) have been filed by Gilead for this and other patent applications. This means that although the patent was not granted, the patent applications are still pending before the patent office.^{116, 117}

The same is true in Brazil, where an estimated 37,000 PLHA are on TDF-based therapies. In April 2008, the government declared tenofovir as a medicine of public interest for priority examination purposes. The National Institute on Industrial Property (INPI – Brazilian patent office) published the patent rejection for TDF on 30 June 2009. However, Gilead has requested a divisional

patent, which has been opposed by civil society groups. In addition, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent.

In Brazil, Gilead has also filed a patent application for the fixed-dose combination TDF/FTC. If the patent is granted, generic competition will be stifled on any essential combination including TDF/FTC, be it as a double fixed-dose combination or as a triple fixed-dose combination, with for example efavirenz, lopinavir or atazanavir. Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with 11 generic manufacturers in India and South Africa, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.¹⁰³

Manufacturers that have signed these agreements are unable to supply countries such as Brazil and China, leaving these countries unable to benefit from competitive prices and improve access. After negotiation with Gilead, Brazil is today paying \$715 per patient per year for tenofovir, over eight times the best available generic price.¹²⁹

Such licensing agreements can contribute to increased competition and improved access to affordable medicines, but should also be offered to manufacturers outside India, and should not include geographic market limitations.

Paediatrics

Tenofovir is approved for adolescents from 12 years old. However, no paediatric fixed-dose combination has been developed with tenofovir and emtricitabine.

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

GENERAL INFORMATION

- Therapeutic class: one NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- Indicated for first-line for adults and adolescents.⁸
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb/Merck, Atripla.
- First approval by U.S. Food and Drug Administration (FDA): July 2006.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- World sales of the originator: 2009: US\$ 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).⁹⁶
- Most patents related to tenofovir (TDF), emtricitabine (FTC), TDF/FTC or to efavirenz (EFV) also affect this combination. In addition, Gilead and BMS jointly applied for patents specifically related to this combination in 2006,⁵⁹ which would last until 2026.
- Gilead pays royalties to BMS (and consequently Merck) for the EFV portion, originally owned by Dupont Merck, which was subsequently acquired by BMS.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

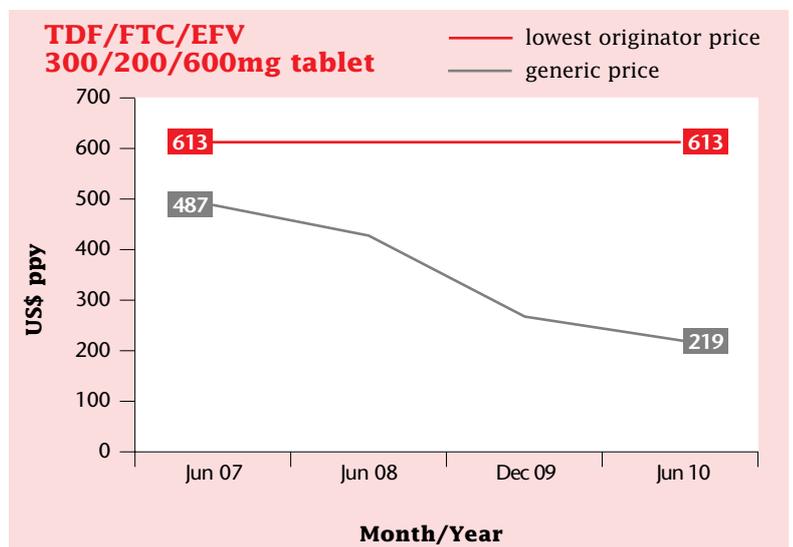
	Daily dose	Gilead/BMS/Merck		Cipla	Matrix (CF)
		Category 1 countries	Category 2 countries		
Who can access this price?		See annex 2 & annex 10		No restrictions	
TDF/FTC/EFV 300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	268 (0.733)	219 (0.600)

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

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

As of April 2010, there was one generic source of TDF/FTC/EFV 300/200/600mg tablet included in the WHO List of Prequalified Medicinal Products. Its price is shown here.

Over very short time, since 2007, the generic price has decreased by 55%, while the originator price has remained the same.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.⁹

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

It is time, however, for countries to invest in a more robust, TDF-based first-line regimen, such as TDF/FTC/EFV (or TDF/3TC/EFV). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.⁹

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

Today, there is one generic source of TDF/FTC/EFV which is included in the WHO List of Prequalified Medicinal Products.

Patents

This combination is produced by Indian generic companies because none of the individual components

is patented in India today. However, Gilead has applied for patents related to TDF, including the one specifically related to this combination.¹⁷⁶ If these patents are granted in India, generic competition for this product may be affected.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. 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. Further, combinations of known molecules are not patentable under Indian patent law.^{174, 175, 176}

Nevertheless, divisional applications (a type of patent application which contains matter from a previously filed application) have been filed by Gilead for this and other patent applications. This means that although the patent was not granted, the patent applications are still pending before the patent office.^{116, 117}

The same is true in Brazil, where an estimated 37,000 PLHA are on TDF-based therapies. In April 2008, the government declared tenofovir as a medicine of public interest for priority examination purposes. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on 30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent. In addition, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent.

In Brazil, Gilead has also filed a patent application for the fixed-dose combination TDF/FTC. If the patent is granted, generic competition will be stifled on any essential combination including TDF/FTC, be it as a double fixed-dose combination or as a triple fixed-dose combination, with for example efavirenz, lopinavir or atazanavir.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with 11 generic manufacturers in India and one in South Africa, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.¹⁰³

Manufacturers that have signed these agreements are unable to supply countries such as Brazil and China, leaving these countries unable to benefit from competitive prices and improve access. After negotiation with Gilead, Brazil is today paying US\$ 715 per patient per year for tenofovir, over eight times the best available generic price.¹²⁹

Such licensing agreements can contribute to increased competition and improved access to affordable medicines, but should also be offered to manufacturers outside India, and should not include geographic market limitations.

Paediatrics

Tenofovir is approved for adolescent from 12 years old. However, no paediatric fixed-dose combination has been developed with tenofovir, emtricitabine and efavirenz.

TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

GENERAL INFORMATION

- Therapeutic class: NtRTI + NRTI in a double fixed-dose combination.
- Indicated for first- and second-line for adults and adolescents.⁸
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- Most patents related to tenofovir (TDF) or to lamivudine (3TC) also affect this combination. In addition, other patents may have been applied for, more specifically related to the use of these medicines in combination, or to this specific FDC, such as by Cipla.¹⁷⁷

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

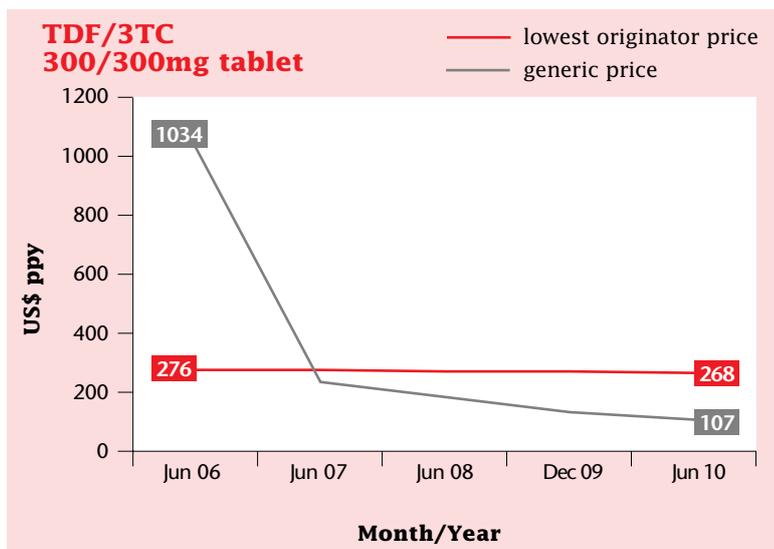
	Daily dose	Cipla	Hetero (CF)	Matrix (CF)
Who can access this price?		No restrictions		
TDF/3TC 300/300mg tablet	1	122 (0.333)	128 (0.350)	107 (0.294)

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

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

As of April 2010, there were two generic sources of TDF/3TC 300/300mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here. As there is no originator fixed-dose combination the price shown for the originator product is the sum of the two individual originator products.

Since 2006, the generic price has dropped by 90% while the combined originator price of the two individual products has decreased by 3%. The most affordable generic FDC is 60% less expensive than the sum of the originator products.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine (AZT) or tenofovir-based (TDF) first-line regimens.⁹

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

It is however time for countries to invest in a more robust, TDF-based first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill once a day. While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.⁹

For second-line treatment, TDF in combination with lamivudine (3TC) or emtricitabine (FTC) are the recommended NRTI backbones, to be added to a boosted protease inhibitor, if stavudine or zidovudine have been used in the first-line regimen.

TDF is also active against Hepatitis B Virus (HBV) and therefore plays an important role in co-infected patients. For HIV patients also requiring treatment for Hepatitis B, the first- and second-line treatment should contain TDF and either 3TC or FTC.

Today, there are two generic sources of this combination included in the WHO List of Prequalified Medicinal Products.

Patents

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead has applied for patents related to TDF. If these patents are granted in India, generic competition for this product may be affected.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. 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. Further, combinations of known molecules are not patentable under Indian patent law.^{174, 175, 176}

Nevertheless, divisional applications (a type of patent application which contains matter from a previously filed application) have been filed by Gilead for this and other patent applications. This means that although the patent was not granted, the patent applications are still pending before the patent office.^{116, 117}

The same is true in Brazil, where an estimated 37,000 PLHA are on TDF-based therapies. In April 2008, the government declared tenofovir as a medicine of public interest for priority examination purposes. The National Institute on Industrial Property (INPI – Brazilian patent office) published the patent rejection for TDF on 30 June 2009. However, Gilead has requested a divisional

patent, which has been opposed by civil society groups. In addition, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with 11 generic manufacturers in India and one in South Africa, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.¹⁰³

Manufacturers that have signed these agreements are unable to supply countries such as Brazil and China, leaving these countries unable to benefit from competitive prices and improve access. After negotiation with Gilead, Brazil is today paying US\$ 715 per patient per year for tenofovir, over eight times the best available generic price.¹²⁹

Such licensing agreements can contribute to increased competition and improved access to affordable medicines, but should also be offered to manufacturers outside India, and should not include geographic market limitations.

Paediatrics

Tenofovir is approved for adolescents from 12 years old. However, no paediatric fixed-dose combination has been developed with tenofovir and lamivudine.

The Paediatric Antiretroviral Working Group of WHO considers the development of a fixed-dose combination of TDF/3TC 75/75mg tablet and a scored 300/300mg tablet to be a high priority.¹³⁷

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

GENERAL INFORMATION

- Therapeutic class: one NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- Indicated for first-line for adults and adolescents.⁸
- Included in 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- Most patents related to tenofovir (TDF), lamivudine (3TC) or to efavirenz (EFV) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination, or to this specific FDC.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet co-pack. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

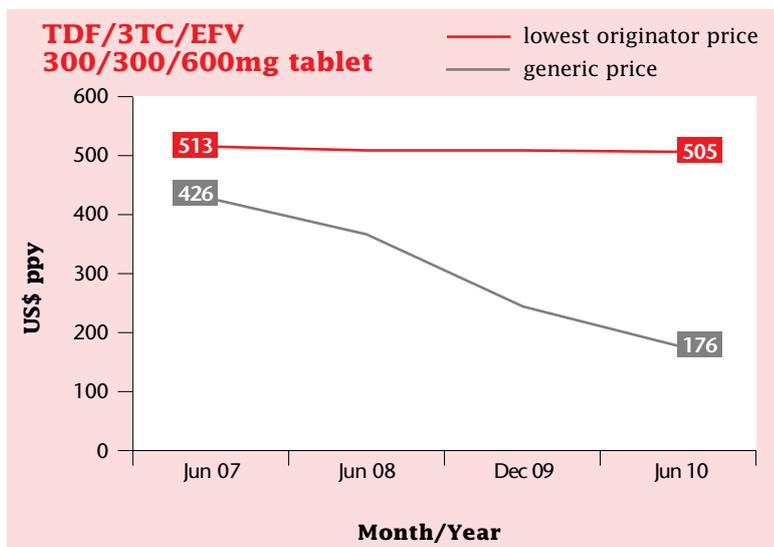
	Daily dose	Cipla	Matrix (CF)
Who can access this price?		No restrictions	
TDF/3TC/EFV 300/300/600mg tablet	1	219 (0.600)	176 (0.483)

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

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

As of April 2010, there was one generic source of TDF/3TC/EFV 300/300/600mg tablet included in the WHO List of Prequalified Medicinal Products. Its price is shown here. As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Over very short time, since 2007, the generic price has dropped by 59%.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.⁹

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

It is time, however, for countries to invest in a more robust, TDF-based first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill once a day. While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.⁹

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

Today, there is one generic source of TDF/3TC/EFV included in the WHO List of Prequalified Medicinal Products.

Patents

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead has applied for patents related to TDF. If these patents are granted in India, generic competition for this product may be affected.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. 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. Further, combinations of known molecules are not patentable under Indian patent law.^{174, 175, 176}

Nevertheless, divisional applications (a type of patent application which contains matter from a previously filed application) have been filed by Gilead for this and other patent applications. This means that although the patent was not granted, the patent applications are still pending before the patent office.^{116, 117}

The same is true in Brazil, where an estimated 37,000 PLHA are on TDF-based therapies. In April 2008, the government declared tenofovir as a medicine of public interest for priority examination purposes. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on

30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with 11 generic manufacturers in India and one in South Africa, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.¹⁰⁸

Manufacturers that have signed these agreements are unable to supply countries such as Brazil and China, leaving these countries unable to benefit from competitive prices and improve access. After negotiation with Gilead, Brazil is today paying US\$ 715 per patient per year for tenofovir, over eight times the best available generic price.¹²⁹

Such licensing agreements can contribute to increased competition and improved access to affordable medicines, but should also be offered to manufacturers outside India, and should not include geographic market limitations.

Paediatrics

Tenofovir is approved for adolescent from 12 years old. However, no paediatric fixed-dose combination has been developed with tenofovir, lamivudine and efavirenz.

ZIDOVUDINE/ LAMIVUDINE (AZT/3TC)

GENERAL INFORMATION

- Therapeutic class: two NRTIs in double fixed-dose combination.
- Indicated for first- and second-line for adults, adolescents and children.^{8,137}
- Originator company and product brand name: GlaxoSmithKline (GSK), Combivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): September 1997.¹⁷
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- World sales of the originator: 2009: US\$ 649 million; 2008: \$713 million; 2007: \$888 million; 2006: \$1 billion; 2005: \$1.1 billion; 2004: \$1.1 billion.^{77, 78, 79, 80, 81, 82}
- Most patents related to zidovudine (AZT) or to lamivudine (3TC) also affect this combination. In addition, GSK applied for patents specifically related to the use of AZT and 3TC in combination,¹⁷⁸ and for the tablet formulation of the FDC,¹⁷⁹ which are due to expire in 2012 and 2017, respectively.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

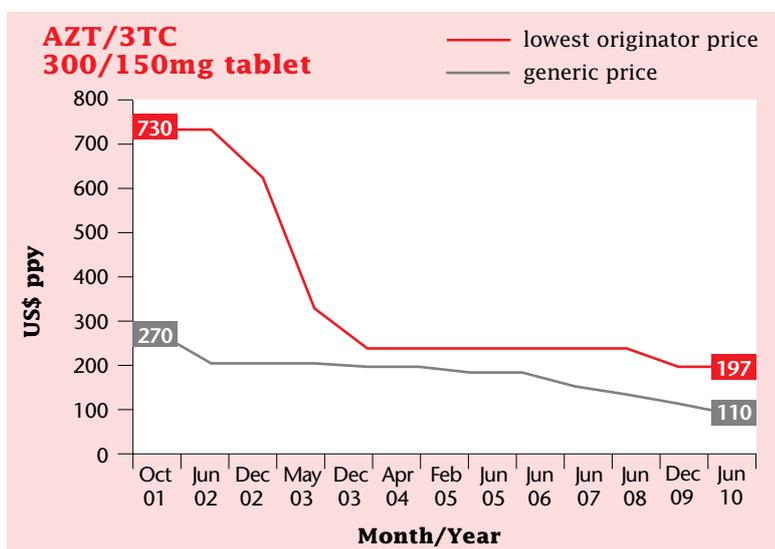
	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		See annex 2	No restrictions					
AZT/3TC 60/30mg tablet	4		95 (0.065)			121 (0.083)	88 (0.060)	
AZT/3TC 300/150mg tablet	2	197 (0.270)	112 (0.154)	111 (0.152)	115 (0.158)	110 (0.150)	110 (0.150)	131 (0.180)

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

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

As of April 2010, there were nine generic sources of AZT/3TC 300/150mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here.

Competition among WHO prequalified sources continues, and has led to a steady decrease in prices of the originator product by 73% and the generic by 59% since 2001.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.⁹

For second-line treatment, AZT in combination with lamivudine (3TC) or FTC is the recommended NRTI backbone, to be added to a boosted protease inhibitor, if tenofovir has been used in the first-line regimen.

Patents

Generic versions of this combination were developed in countries where neither of the molecules, nor their combination,

were patented. However, the generic versions of the medicine produced in India came under threat when India began granting patents on pharmaceuticals in 2005, as GlaxoSmithKline (GSK) had applied for a patent on the combination.

Civil society organisations in India opposed the patent application in March 2006,¹²⁷ which resulted in GSK communicating in August 2006 that patents specifically related to the fixed-dose combination were being withdrawn in all countries.¹⁸⁰

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

Paediatrics

The most commonly used first-line regimens for children today are either AZT+3TC+NVP or d4T+3TC+NVP. With both of these regimens, there is a need to start

the NVP at a lower dose for the first two weeks to minimise the side effects.

Quality-assured double fixed-dose combinations are therefore of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer. Today, there are two paediatric AZT/3TC fixed-dose combination tablets included in the WHO List of Prequalified Medicinal Products.

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

GENERAL INFORMATION

- Therapeutic class: three NRTIs in triple fixed-dose combination.
- Indicated under specific conditions in adults, adolescents and children.^{8, 137}
- 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.²⁶
- Originator company and product brand name: GlaxoSmithKline (GSK), Trizivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 2000.¹⁷
- World sales of originator product: 2009: US\$ 307 million; 2008: \$350 million; 2007: \$455 million; 2006: \$529 million; 2005: \$598 million; 2004: \$635 million.^{77, 78, 79, 80, 81, 82}
- Most patents on zidovudine (AZT), lamivudine (3TC), AZT/3TC or abacavir (ABC) also affect this combination. In addition, GSK applied for patents more specifically related to the triple combination.¹⁷³

PRICE INFORMATION

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

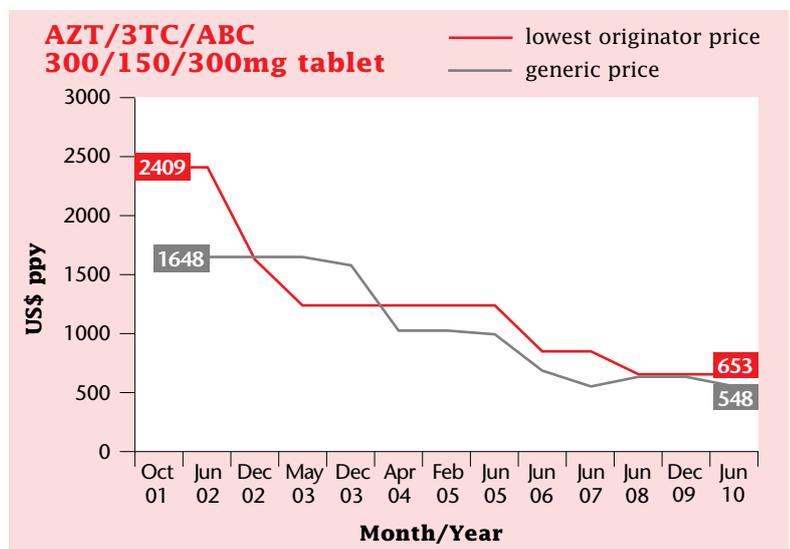
The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	ViiV	Cipla	Matrix	Ranbaxy
Who can access this price?		See annex 2			
AZT/3TC/ABC 60/30/60 mg tablet	4			244 (0.167)	
AZT/3TC/ABC 300/150/300 mg tablet	2	653 (0.895)	414 (0.567)	365 (0.500)	548 (0.750)

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

As of April 2010, there was one generic source of AZT/3TC/ABC 300/150/300mg tablet included in the WHO List of Prequalified Medicinal Products. Its price is shown here.

There has been a decrease of 67% in the generic price and 73 % in the originator price since 2001.



SPOTLIGHT ON ACCESS ISSUES

This FDC is the only triple NRTI formulation available.

This combination is no longer a preferred regimen in the developed world.¹⁸¹

In the developing world, its use is limited to individuals with contraindication to NNRTI-based regimens or who are unable to tolerate them. This applies particularly for people co-infected with TB/HIV, pregnant women, patients with chronic viral Hepatitis and those with HIV-2 infection.¹³⁷

Patents

GlaxoSmithKline (GSK) could not apply for basic patents related to

abacavir (ABC), zidovudine (AZT) or lamivudine (3TC) in some developing countries such as India, which did not grant patents on pharmaceuticals at the time. This allowed Indian generic companies to develop generic versions of each medicine, and of the combination.

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

In India, GSK had applied for patents more specifically related to the fixed-dose combination. The company withdrew the patent application after a pre-grant opposition was filed in 2006.¹⁸²

Paediatrics

The paediatric formulation of AZT/3TC/ABC is a generic version and is now included in the WHO List of Prequalified Medicinal Products.

However, this product is not commercially available yet because there is not enough market demand to make the product commercially viable.

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

GENERAL INFORMATION

- Therapeutic class: two NRTI + one NNRTI in triple fixed-dose combination.
- Indicated for first-line for adults, adolescents and children.^{8,137}
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).²⁶
- 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.²⁶
- Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to nevirapine (NVP) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination, or for this specific FDC.

PRICE INFORMATION

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

The price in brackets corresponds to the price of one tablet. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

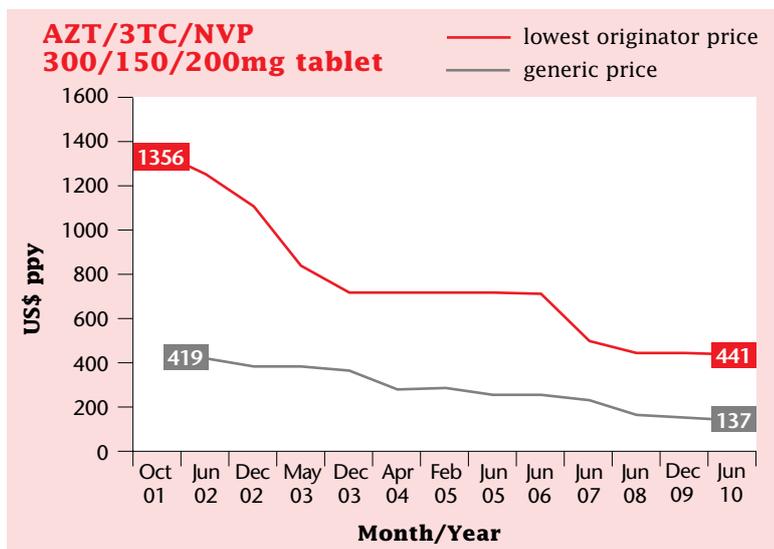
	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		No restrictions					
AZT/3TC/NVP 60/30/50mg dispersible tablet	4				158 (0.108)	183 (0.125)	
AZT/3TC/NVP 300/150/200mg tablet	2	148 (0.203)	137 (0.188)	155 (0.213)	143 (0.196)	145 (0.199)	139 (0.190)

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

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

As of April 2010, there were six generic sources of AZT/3TC/NVP 300/150/200mg tablet included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here. As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Generic prices have steadily decreased by 67% since 2002.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.⁹

Patents

In addition to the generic manufacturers referenced above, Apotex also manufactures an AZT/3TC/NVP fixed-dose combination¹⁸³ for export to developing countries under the 30 August 2003 World Trade Organization decision on compulsory licensing for export.¹⁸⁴

In early 2004, MSF made the original request for the development of this FDC to Apotex, as no generic versions of the FDC were available at the time.¹⁸⁵

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

Paediatrics

The most-commonly used first-line regimens for children today are either AZT+3TC+NVP or d4T+3TC+NVP.

Today there is only one generic paediatric AZT/3TC/NVP fixed-dose combination included in the WHO List of Prequalified Medicinal Products.

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

GENERAL INFORMATION

- Therapeutic class: two NRTI + one NNRTI in a co-pack.
- Indicated for first-line for adults, adolescents and children.^{8,137}
- 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.²⁶
- Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to efavirenz (EFV) also affect this combination. In addition, Cipla applied for patents specifically related to the use of AZT, 3TC and EFV in combination.¹⁸⁶

PRICE INFORMATION

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

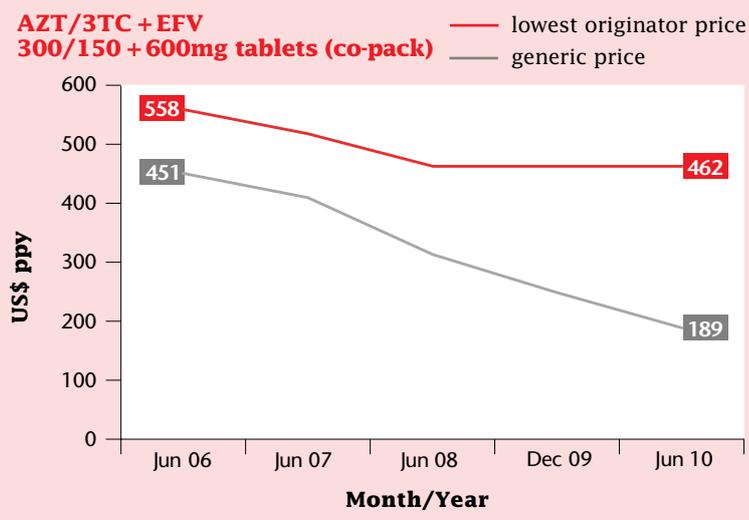
The price in brackets corresponds to the price of one kit (3 tablets). Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

	Daily dose	Aurobindo	Cipla	Ranbaxy	Strides
Who can access this price?		No restrictions			
AZT/3TC + EFV 300/150 + 600mg tablets (co-pack)	1 kit (3 tablets)	231 (0.633)	320 (0.877)	322 (0.883)	189 (0.517)

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

As of April 2010, there were three generic sources of AZT/3TC + EFV 300/150 + 600mg tablets (co-pack) included in the WHO List of Prequalified Medicinal Products. The one with the lowest price is shown here. As there is no originator co-pack, the price shown for the originator product is the sum of the two individual originator products.

Since 2006, the price of generic has dropped by 58%.



SPOTLIGHT ON ACCESS ISSUES

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries

to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.

In addition, efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on TB treatment.⁹

Patents

Basic patents related to zidovudine (AZT), lamivudine (3TC) or efavirenz (EFV) could not be obtained in some

developing countries such as India, which did not grant product patents on pharmaceuticals at the time.

This allowed Indian drug companies to manufacture generic versions of the medicines and to develop this product.

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

ANNEX 1: SUMMARY TABLE - ALL PRICES ON ONE PAGE**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 April 2010) are in **bold**.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies					
Abacavir (ABC)		ViiV		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
20mg/ml oral solution	10 ml	230 (0.063/ml)		212 (0.058/ml)	113 (0.031/ml)				
60mg tablet	4			153 (0.105)	134 (0.092)		183 (0.125)		540 (0.370)
300mg tablet	2	438 (0.600)		243 (0.333)	207 (0.283)	256 (0.350)	219 (0.300)	274 (0.375)	
Atazanavir (ATV)*		BMS		Matrix					
		Category 1 countries	Category 2 countries						
150mg capsule	2	353 (0.484)	431 (0.590)						
200mg capsule	xx	(0.602)	(0.743)						
300mg capsule	1			256 (0.700)					
Darunavir (DRV)*		Tibotec							
300mg tablet	4	1095 (0.750)							
Didanosine (ddl)		BMS		Aurobindo	Cipla	Ranbaxy			
		Category 1 countries	Category 2 countries						
2g powder for reconstitution (final concentration 10mg/ml)	12 ml	276 (12.590/2g)	308 (14.057/2g)	88 (4.000/2g)					
25mg tablet	5	212 (0.116)	429 (0.235)		115 (0.063)	228 (0.125)			
50mg tablet	xx	(0.158)	(0.235)		(0.079)	(0.115)			
100mg tablet	4	311 (0.213)	364 (0.249)	194 (0.133)	188 (0.129)	242 (0.166)			
125mg enteric-coated capsule	1			110 (0.300)					
150mg tablet	xx	(0.308)	(0.345)	(0.225)	(0.167)				
200mg tablet	xx			(0.267)	(0.257)				
200mg enteric-coated capsule	xx			(0.383)					
250mg enteric-coated capsule	1	223 (0.611)	249 (0.683)	170 (0.467)	103 (0.283)				
400mg enteric-coated capsule	1	288 (0.789)	322 (0.881)	256 (0.700)	132 (0.363)				
Efavirenz (EFV)		Merck		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
30mg/ml suspension	xx	(0.094/ml)	(0.151/ml)						
50mg capsule	xx			(0.083)					
50mg tablet	xx	(0.120)	(0.210)				(0.083)		
100mg capsule	xx			(0.150)					
200mg capsule	3			130 (0.119)	134 (0.122)	152 (0.139)		118 (0.108)	
200mg tablet	3	394 (0.360)	821 (0.750)				146 (0.133)		110 (0.100)
600mg tablet	1	237 (0.650)	657 (1.800)	73 (0.200)	79 (0.217)	82 (0.225)	61 (0.167)	91 (0.250)	62 (0.170)

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

ARVs in alphabetical order	Daily dose	Originator company		Generic companies						
Emtricitabine (FTC)				Aurobindo	Matrix					
200mg capsule	1			63 (0.173)	79 (0.217)					
Etravirine (ETV)		Tibotec								
100mg tablet	4	913 (0.625)								
Fosamprenavir (FPV)*		ViiV								
50mg/ml suspension	12ml	648 (0.148/ml)								
700mg tablet	2	1222 (1.674)								
Indinavir (IDV)*		Merck								
		Category 1 countries	Category 2 countries	Aurobindo	Cipla	Hetero				
400mg capsule	4	394 (0.270)	686 (0.470)	292 (0.200)	422 (0.289)	390 (0.267)				
Lamivudine (3TC)		ViiV		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides	
10mg/ml oral solution	10ml	84 (0.023/ml)		29 (0.008/ml)	37 (0.010/ml)	37 (0.010/ml)				
150mg tablet	2	64 (0.087)		34 (0.047)	35 (0.048)	33 (0.045)	34 (0.046)	34 (0.047)	37 (0.050)	
300mg tablet	1			24 (0.067)	41 (0.113)	38 (0.103)	34 (0.092)			
Lopinavir/ritonavir (LPV/r)		Abbott								
		Category 1 countries	Category 2 countries	Aurobindo	Cipla	Hetero	Matrix			
80/20mg/ml oral solution	4ml	176 (0.121/ml)		400 (0.274/ml)						
100/25mg heat-stable tablet	3	165 (0.151)		376 (0.343)	219 (0.200)		228 (0.208)			
133/33mg soft-gel capsule	6	500 (0.228)		1000 (0.457)		609 (0.278)				
200/50mg heat-stable tablet	4	440 (0.301)		1000 (0.685)	475 (0.325)	463 (0.317)	493 (0.338)	486 (0.333)		
Nelfinavir (NFV)		Roche								
		Category 1 countries	Category 2 countries	Cipla						
50mg/g oral powder	24g	2129 (0.243/g)		2462 (0.281/g)						
250mg tablet	10	1566 (0.429)		2427 (0.665)	945 (0.259)					
Nevirapine (NVP)		Boehringer								
		Category 1 countries	Category 2 countries	Aurobindo	Cipla	Hetero	Huahai	Matrix	Ranbaxy	Strides
10mg/ml suspension	20ml	380 (0.052/ml)		533 (0.073/ml)	66 (0.009/ml)	73 (0.010/ml)				
200mg tablet	2	219 (0.300)		438 (0.600)	39 (0.054)	34 (0.046)	37 (0.050)	34 (0.047)	39 (0.054)	39 (0.053)
Raltegravir (RAL)		Merck								
		Category 1 countries								
400mg tablet	2	1113 (1.525)								

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

ARVs in alphabetical order	Daily dose	Originator company		Generic companies					
Ritonavir (RTV)		Abbott		Cipla					
		Category 1 countries							
80mg/ml oral solution	xx	(0.093/ml)							
100mg soft-gel capsule	2	83 (0.114)		323 (0.442)					
100mg heat-stable tablet	2	83 (0.114)							
Saquinavir (SQV)*		Roche		Cipla					
		Category 1 countries	Category 2 countries						
200mg hard capsule	10	1212 (0.332)	2427 (0.665)	1621 (0.444)					
500mg tablet	4	1113 (0.762)	2427 (1.662)						
Stavudine (d4T)		BMS		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
1mg/ml powder for oral solution	20 ml	51 (0.007/ml)	58 (0.008/ml)	58 (0.008/ml)	44 (0.006/ml)				
15mg capsule	xx	(0.082)	(0.093)	(0.026)	(0.024)	(0.025)			
20mg capsule	xx	(0.089)	(0.093)	(0.027)	(0.025)	(0.028)			
30mg capsule	2	48 (0.066)	68 (0.093)	20 (0.028)	26 (0.035)	21 (0.029)	24 (0.033)	26 (0.035)	22 (0.030)
Tenofovir (TDF)		Gilead		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
300mg tablet	1	204 (0.559)	360 (0.986)	100 (0.275)	87 (0.237)	103 (0.283)	85 (0.233)	152 (0.417)	146 (0.400)
Zidovudine (AZT)		ViiV		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	
10mg/ml oral solution	20 ml	234 (0.032/ml)		66 (0.009/ml)	80 (0.011/ml)	66 (0.009/ml)			
60mg tablet	4			115 (0.079)					
100mg capsule	xx	(0.122)		(0.051)	(0.050)				
250mg capsule	xx	(0.276)							
300mg tablet	2	161 (0.221)		101 (0.138)	97 (0.133)	100 (0.137)	91 (0.125)	91 (0.125)	
ABC/3TC		ViiV		Aurobindo	Cipla	Matrix			
60/30mg tablet	4			175 (0.120)		244 (0.167)			
600/300mg tablet	1	484 (1.326)		134 (0.367)	152 (0.417)				
3TC/d4T				Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
30/6mg dispersible tablet	4				47 (0.032)				
60/12mg dispersible tablet	2				40 (0.055)				
150/30mg tablet	2			50 (0.068)	42 (0.057)	51 (0.070)	42 (0.058)	42 (0.058)	44 (0.060)
3TC/d4T/NVP				Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
30/6/50mg dispersible tablet	4				55 (0.038)				
60/12/100mg dispersible tablet	2				53 (0.072)				
150/30/200mg tablet	2			67 (0.092)	67 (0.092)	73 (0.100)	67 (0.092)	70 (0.096)	73 (0.100)

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

ARVs in alphabetical order	Daily dose	Originator company		Generic companies					
3TC/d4T + EFV				Cipla	Ranbaxy	Strides			
150/30 + 600mg tablets (co-pack)	1 kit (3 tabs)			274 (0.751)	304 (0.833)	106 (0.290)			
TDF/FTC		Gilead		Aurobindo	Cipla	Hetero	Matrix		
		Category 1 countries	Category 2 countries						
300/200mg tablet	1	315 (0.863)	540 (1.479)	155 (0.425)	158 (0.433)	164 (0.450)	143 (0.392)		
TDF/FTC/EFV		BMS/Gilead/Merck		Cipla	Matrix				
		Category 1 countries	Category 2 countries						
300/200/600mg tablet	1	613 (1.680)	1033 (2.830)	268 (0.733)	219 (0.600)				
TDF/3TC				Cipla	Hetero	Matrix			
300/300mg tablet	1			122 (0.333)	128 (0.350)	107 (0.294)			
TDF/3TC/EFV				Cipla	Matrix				
300/300/600mg tablet	1			219 (0.600)	176 (0.483)				
AZT/3TC		ViiV		Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
60/30mg tablet	4			95 (0.065)			121 (0.083)	88 (0.060)	
300/150mg tablet	2	197 (0.270)		112 (0.154)	111 (0.152)	115 (0.158)	110 (0.150)	110 (0.150)	131 (0.180)
AZT/3TC/ABC		ViiV		Cipla	Matrix	Ranbaxy			
60/30/60mg tablet	4				244 (0.167)				
300/150/300mg tablet	2	653 (0.895)		414 (0.567)	365 (0.500)	548 (0.750)			
AZT/3TC/NVP				Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides
60/30/50mg dispersible tablet	4						158 (0.108)	183 (0.125)	
300/150/200mg dispersible tablet	2			148 (0.203)	137 (0.188)	155 (0.213)	143 (0.196)	145 (0.199)	139 (0.190)
AZT/3TC + EFV				Aurobindo	Cipla	Ranbaxy	Strides		
300/150+600mg tablets (co-pack)	1 kit (3 tabs)			231 (0.633)	320 (0.877)	322 (0.883)	189 (0.517)		

ANNEX 2: CONDITIONS OF OFFER BY COMPANY

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
Abbott	<p>Category 1 countries: All African countries and all United Nations defined Least-Developed Countries outside Africa.</p> <p>Category 2 countries: See Annex 8 for more details.</p>	Governments and programmes fully funded by governments, UN systems organisations, NGOs and other not-for-profit institutional providers in low- and lower middle-income countries.		FOB
Aurobindo	No reported restrictions.	NGOs and governmental organisations.	<p>Prices available for above 500,000 units for tablet packs and above 10,000 units for oral solutions.</p> <p>Delivery of goods four to six weeks from the date of confirmed orders.</p>	<p>Payment by letter of credit.</p> <p>FOB Hyderabad (India).</p>
Boehringer Ingelheim (BI)	<p>Category 1 countries: All LDCs, all low-income countries and all of Africa</p> <p>Category 2 countries: All middle-income countries not covered under category 1.</p>	Governments, NGOs and other partners who can guarantee that the programme is run in a responsible manner.		CIF
Bristol-Myers Squibb (BMS)	<p>Category 1 countries: Sub-Saharan African countries (except southern African countries) plus countries classified as low-income by the World Bank (except Korea, Kyrgyzstan, Moldova and Uzbekistan).</p> <p>Category 2 countries: Southern African countries. See annex 7 for more details.</p> <p>For other developing countries, prices are negotiated on a case-by-case basis with BMS local representatives.</p>	Both private and public sector organisations that are able to provide effective, sustainable and medically-sound care and treatment of HIV/AIDS.	<p>Category 1 countries are invoiced in US\$.</p> <p>Category 2 countries are invoiced in South African Rand.</p>	CIP incoterm.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
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 (India) or CIF. The actual freight is charged separately.
Gilead	There are over 130 eligible countries, including all African states and additional countries classified as low- or lower middle-income based on a country's economic status measure by gross national income (GNI) and HIV prevalence. See Annex 9 for more details. For other countries, prices are negotiated on a case-by-case basis.	Organisations that provide HIV treatment in 130 countries are covered by the Gilead Access Program.	The Program is managed through Gilead's International Access Operations and Gilead's local distribution partners. Please note that local taxes, tariffs, and limited distributor mark-ups may be added to the ex-factory prices.	Shipping terms vary by local distributor.
Hetero	No reported restrictions.	Private sector, public sector and NGOs.	Prices may be negotiated on individual basis according to commercial terms.	FOB Mumbai (India).
Huahai	No reported restrictions.	Governments, non-profit institutional providers of HIV care, NGOs, and other private and public organisations that are able to provide responsible, sustainable and medically sound care.	For final purchase, price will be further negotiated, considering the factors like changes in exchange rate.	FCA Shanghai.
Matrix	No reported restrictions except Cuba, Iran, North Korea, Syria, Sudan, Belarus, Myanmar, DR Congo and Liberia, for which prior approval from Mylan Labs Inc is required.	No restrictions.	Minimum order – One full shipper / carton packs.	Ex-works Nashik, India or as specified by customers.
Merck	Please refer to Annex 10 for the individual drug country eligibility.	Governments, international organisations, NGOs, private sector organisations (e.g. employers, hospitals and insurers).	Merck may under certain circumstances supply ARVs to patients through retail pharmacies.	CIP
Ranbaxy	No reported restrictions, but higher prices were negotiated separately for 10 Latin American countries.	NGOs and governments or programmes supported by them.	Confirmed letter of credit or advance payment preferred for new customers.	FOB Delhi (India).

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

NOTES:

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

This lack of uniformity leads to significant differences in the eligibility of a country for different products.

For complete details please refer to annexes 3-10.

ANNEX 3: LEAST-DEVELOPED COUNTRIES (LDCS)

Source: United Nations

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

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

ANNEX 4: HUMAN DEVELOPMENT INDEX (HDI)

Source: United Nations Development Programme (UNDP)

http://hdr.undp.org/en/media/hdr_20072008_en_complete.pdf

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

Low human development:

Afghanistan; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Congo DRC; Côte d'Ivoire; Eritrea; Ethiopia; Gambia; Guinea; Guinea-Bissau; Liberia; Malawi; Mali; Mozambique; Niger; Rwanda; Senegal; Sierra Leone; Timor-Leste; Togo; Zambia.

Medium human development:

Algeria; Angola; Armenia; Azerbaijan; Bangladesh; Belize; Bhutan; Bolivia; Botswana; Cambodia; Cameroon; Cape Verde; China; Comoros; Congo; Djibouti; Dominican Republic; Egypt; El Salvador; Equatorial Guinea; Fiji; Gabon; Georgia; Ghana; Guatemala; Guyana; Haiti; Honduras; India; Indonesia; Iran; Jamaica; Jordan; Kenya; Kyrgyzstan; Lao PDR; Lesotho; Madagascar; Maldives; Mauritania; Moldova; Mongolia; Morocco; Myanmar; Namibia; Nepal; Nicaragua; Nigeria; Pakistan; Occupied Palestinian Territories; Papua New Guinea; Paraguay; Philippines;

St. Vincent and the Grenadines; Samoa; São Tomé and Príncipe; Solomon Islands; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syria; Tanzania; Tajikistan; Thailand; Tonga; Tunisia; Turkmenistan; Uganda; Ukraine; Uzbekistan; Vanuatu; Viet Nam; Yemen.

ANNEX 5: SUB-SAHARAN COUNTRIES

Source: World Bank country classification

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

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

ANNEX 6: WORLD BANK CLASSIFICATION OF ECONOMIES

Source: World Bank

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

The list is updated every year on 1 July. This version is effective from 1 July 2009.

Low-income economies:

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

Lower middle-income economies:

Albania; Angola; Armenia; Azerbaijan; Belize; Bhutan; Bolivia; Cameroon; Cape Verde; China; Congo; Djibouti; Ecuador; Egypt; El Salvador; Georgia; Guatemala; Guyana; Honduras; India; Indonesia; Iran; Iraq; Jordan; Kiribati; Kosovo; Lesotho; Maldives; Marshall Islands; Micronesia; Moldova; Mongolia; Morocco; Nicaragua; Nigeria; Pakistan; Occupied Palestinian Territories; Papua New Guinea; Paraguay; Philippines; Samoa; São Tomé and Príncipe; Solomon Islands; Sri Lanka; Sudan; Swaziland; Syria; Thailand; Timor-Leste; Tonga; Tunisia; Turkmenistan; Ukraine; Vanuatu.

Upper middle-income economies:

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

ANNEX 7: BRISTOL-MYERS SQUIBB ELIGIBLE COUNTRIES

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

1st Category Countries:

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; India; Kenya; Lao PDR; 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; Sudan; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Viet Nam; Yemen.

2nd Category Countries: Southern African countries:

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

ANNEX 8: ABBOTT ELIGIBLE COUNTRIES

Source: Abbott's Access to HIV Care Program

1st Category Countries: Africa and Least-Developed countries:

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

2nd Category Countries:

Low-Income economies (excluding Africa and the LDC as defined by the UN):

India; Kyrgyzstan; Mongolia; Pakistan; Papua New Guinea; Tajikistan; Uzbekistan; Viet Nam.

Lower Middle-Income economies (excluding Africa and the LDC as defined by the UN):

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

ANNEX 9: GILEAD ELIGIBLE COUNTRIES

Source: Gilead Access Program

http://www.gilead.com/enabling_access

1st Category Countries:

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

2nd Category Countries:

Lower Middle-Income Pricing Tier
Albania; Armenia; Azerbaijan; Belarus; Bosnia and Herzegovina; China; Ecuador; El Salvador; Fiji; Georgia; Iran; Iraq; Jordan; Kazakhstan; Montenegro; Panama; Paraguay; Peru; Philippines; Serbia; Sri Lanka; Thailand; Tonga; Turkmenistan.

ANNEX 10: MERCK & CO. INC. ELIGIBLE COUNTRIES

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

Inquiries about pricing for the following countries will be handled on a case-by-case basis: Iraq; Marshall Islands; Micronesia; Montenegro; Nauru; Korea (DPR); Palau.

Merck's Pricing Policy for efavirenz and indinavir

1st Category Countries:

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

2nd Category Countries:

Albania; Algeria; Armenia; Azerbaijan; Belarus; Bolivia; Bosnia Herzegovina; Brazil; Bulgaria; China; Colombia; Costa Rica; Ecuador; Egypt; El Salvador; Estonia; Fiji; Georgia; India; Indonesia; Iran; Jordan; Kazakhstan; Kyrgyzstan; Latvia; Lebanon; Libya; Lithuania; Macedonia; Malaysia; Mauritius; Mexico; Mongolia; Morocco; Nicaragua; Oman; Palestinian Territories; Paraguay; Peru; Philippines; Saudi Arabia; Seychelles; Sri Lanka; Syria; Tajikistan; Tunisia; Turkey; Turkmenistan; Uzbekistan; Venezuela; Viet Nam.

*In Botswana, Merck provides indinavir and efavirenz free of charge.

**Due to a special partnership in Romania, Merck provides indinavir and efavirenz at a 'no-profit price'.

Merck's Pricing Policy for raltegravir

1st Category Countries:

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; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea-Bissau; Guinea; Haiti; Kenya; Kiribati; Lao PDR; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Rwanda; São Tomé and Príncipe; Senegal; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Swaziland; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vanuatu; Western Samoa; Yemen; Zambia; Zimbabwe.

2nd Category Countries:

Algeria; Armenia; Azerbaijan; Belize; Bolivia; Brazil**; China; Colombia; Dominica; Dominican Rep.; Ecuador; Egypt; El Salvador; Fiji; Georgia; Grenada; Guatemala; Guyana; Honduras; India; Indonesia; Iran; Jamaica; Jordan; Kazakhstan; Kyrgyzstan; Lebanon; Moldova; Mongolia; Morocco; Nicaragua; Pakistan; Palestinian Territories; Peru; Philippines; St. Lucia; St. Vincent and the Grenadines; Sri Lanka; Suriname; Syria; Tajikistan; Thailand; Tunisia; Turkey; Turkmenistan; Ukraine; Uzbekistan; Venezuela; Viet Nam.

*In Botswana, Merck provides raltegravir free of charge.

**Merck notes that Brazil 'receives significant reduced pricing due to extraordinary commitment in treating HIV/AIDS patients.'

Merck's Pricing Policy for TDF/FTC/EFV 300/200/600mg

1st Category Countries:

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

2nd Category Countries:

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

ANNEX 11: SUGGESTED RESOURCES FOR FURTHER INFORMATION:

For documentation on prices quoted by companies:

Untangling the Web can also be found online at utw.msfacecess.org

Back issues of Untangling the Web of price reductions: a pricing guide for the purchase of ARVs for developing countries can be found at:

<http://www.msfacecess.org/main/hiv-aids/untangling-the-web/untangling-the-web-archive/>

Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS (June 2005 and 2006) http://www.who.int/medicines/areas/access/med_prices_hiv_aids/en/index.html

Global HIV/Aids Epidemic Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited, January 2005: http://pdf.dec.org/pdf_docs/Pcaab266.pdf

For documentation on prices reported by countries:

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

The Global Fund Purchase Price-Report <http://pqr.theglobalfund.org/PQRWeb/Reports/PurchasePriceReport.aspx>

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

WHO AFRO region Essential Medicines Price Indicator http://www.who.int/medicines/publications/afro-essential_med_price_indicator_nocover.pdf

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://www.who.int/Intellectualproperty/submissions/MSFSubmissionWHO_EPM_PAR_2004.6.pdf

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

'Drug patents under the spotlight. Sharing practical knowledge about pharmaceutical patents' MSF, June 2004. http://www.who.int/3by5/en/patents_2003.pdf

Knowledge Ecology International <http://www.keionline.org>, or <http://www.cptech.org/ip/health/>

For documentation on quality:

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

Approved and 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:

International Dispensary Association (IDA) Price Indicator http://www.idafoundation.org/documents/ida_hiv_aids_aug_07_zondersnijlijnen.pdf

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

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

WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach - 2006 rev. Geneva: WHO; 2006. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>

WHO. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. Geneva: WHO; 2009 Nov. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf

Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a public health approach 2007. <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf>

UNICEF Procurement of HIV/AIDS Related Supplies. September 2007 [http://www.unicef.org/supply/files/Procurement_of_HA_supplies\(1\).pdf](http://www.unicef.org/supply/files/Procurement_of_HA_supplies(1).pdf)

Biotechnology/Pharmaceuticals HIV/AIDS Industry Report – April 2005 <http://www.aethlonmedical.com/pdfs/IndustryReport.pdf>

Clinton Foundation Antiretroviral Price List http://www.clintonfoundation.org/files/chai_arv_priceList_april2010_english.pdf

MSF Campaign for Access to Essential Medicines web site
<http://www.msfacecess.org>

ANNEX 12: COMPANY CONTACTS

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ANNEX 13: THE CLINTON FOUNDATION ANTIRETROVIRAL PRICE LIST (AS OF APRIL 2010)



The Clinton Health Access Initiative (CHAI) supports national governments to expand high-quality care and treatment to people living with HIV/AIDS. CHAI offers reduced prices for antiretrovirals (ARVs) to members of its Procurement Consortium.

SUPPLIERS & PRODUCTS

CHAI has agreements with seven manufacturers of ARV formulations, active pharmaceutical ingredients and/or pharmaceutical intermediates: Aurobindo Pharma, Cipla Ltd., Hetero Drugs, Macleods Pharmaceuticals, 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), 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 license from Gilead, indicated pricing is available only to countries covered under the voluntary license. Please contact Neeraj Mohan at nmohan@clintonfoundation.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 prices represent price ceilings at or below which the indicated suppliers must price their products when selling or communicating price quotes for the specified products to members of the CHAI Procurement Consortium. In establishing price ceilings, CHAI aims to offer the lowest available prices to Consortium members while ensuring that products are available from more than one partner supplier wherever possible. Prices listed below are FCA Airport from the point of export. Per person per year prices 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 on pages 90 and 91, 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.

CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) PRICE LIST

ADULT PRODUCTS		CEILING PRICE (USD)			SUPPLIER					
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Hetero	MacLeods	Matrix	Ranbaxy
3TC (150mg)	HDPE bottle 60 tablets	\$32	\$2.67	\$0.044	✓ ^{1,2}	✓ ¹	✓ ¹	✓ ²		✓ ^{1,2}
ABC (300mg)	HDPE bottle 60 tablets	\$222	\$18.50	\$0.308	✓ ²	✓ ^{1,2}	✓ ⁴		✓ ^{1,2}	
AZT (300mg)	HDPE bottle 60 tablets	\$93	\$7.75	\$0.129	✓ ^{1,2}	✓ ¹	✓ ²		✓ ^{1,2}	✓ ^{1,2}
AZT (300mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$110	\$9.17	\$0.153	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ²		
AZT (300mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$140	\$11.67	\$0.194	✓ ²	✓ ^{1,2}	✓ ^{1,2}			
ATV (300mg)*	HDPE bottle 30 capsules	\$265	\$22.08	\$0.736					✓ ³	
d4T (30mg)	HDPE bottle 60 capsules	\$24	\$2.00	\$0.033	✓ ^{1,2}		✓ ²		✓ ^{1,2}	✓ ¹
d4T (30mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$45	\$3.75	\$0.063	✓ ¹	✓ ^{1,2}			✓ ^{1,2}	
d4T (30mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$79	\$6.58	\$0.110	✓ ¹	✓ ^{1,2}	✓ ¹		✓ ¹	
EFV (600mg)	HDPE bottle 30 tablets	\$75	\$6.25	\$0.208	✓ ^{1,2}				✓ ^{1,2}	
LPV/r (200/50mg)	HDPE bottle 120 tablets	\$440	\$36.67	\$0.306	✓ ²	✓ ²	✓ ⁴		✓ ^{1,2}	
NVP (200mg)	HDPE bottle 60 tablets	\$37	\$3.08	\$0.051	✓ ^{1,2}	✓ ^{1,2}	✓ ^{1,2}	✓ ²	✓ ^{1,2}	✓ ^{1,2}
RTV (100mg) heat-stable*	HDPE bottle 30 tablets	\$90	\$7.50	\$0.250					✓ ⁴	
TDF (300mg)	HDPE bottle 30 tablets	\$87	\$7.25	\$0.242	✓ ²	✓ ^{1,2}	✓ ²		✓ ^{1,2}	
TDF + 3TC (300/300mg)*	HDPE bottle 30 tablets	\$110	\$9.17	\$0.306			✓ ²		✓ ²	
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	\$140	\$11.67	\$0.389	✓ ²				✓ ²	
TDF + 3TC + EFV (300/300/600 mg)	HDPE bottle 30 tablets	\$200	\$16.67	\$0.556					✓ ²	
TDF + FTC + EFV (300/200/600 mg)	HDPE bottle 30 tablets	\$229	\$19.10	\$0.637					✓ ²	

*CHAI has negotiated a price of USD \$425 per person per year for a co-packaged once-daily second-line regimen containing ATV, heat-stable RTV and a fixed dose combination of TDF+3TC. This product is likely to be available for procurement in late 2010.

CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) PRICE LIST

PEDIATRIC PRODUCT		CEILING PRICE (USD)			SUPPLIER			
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Matrix	Strides
3TC (50mg/5ml)	HDPE bottle 240ml	\$25	\$1.65	\$0.007	✓ ²	✓ ^{1,2}		
ABC (20mg/ml)	HDPE bottle 240ml	\$203	\$13.53	\$0.056	✓ ²	✓ ¹		
ABC 60mg	HDPE bottle 60 tablets	\$126	\$5.25	\$0.088	✓ ²		✓ ¹	
ABC (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$168	\$7.00	\$0.117	✓ ²		✓ ¹	
AZT (50mg/5ml)	HDPE bottle 240ml	\$57	\$1.90	\$0.008	✓ ²	✓ ^{1,2}		
AZT (100mg)	HDPE bottle 100 capsules	\$35	\$4.80	\$0.048	✓ ²		✓ ¹	
AZT (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$80	\$3.34	\$0.056	✓ ²		✓ ¹	
AZT (60mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$102	\$4.25	\$0.071			✓ ¹	
d4T (1mg/ml)	HDPE bottle 200ml	\$47	\$1.30	\$0.007	✓ ²	✓ ²		
d4T (15mg)	HDPE bottle 60 capsules	\$16	\$1.35	\$0.023	✓ ²			
d4T (20mg)	HDPE bottle 60 capsules	\$8	\$1.40	\$0.023	✓ ²			
d4T (6mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$46	\$1.90	\$0.032		✓ ²		
d4T (12mg) + 3TC (60mg)	HDPE bottle 60 tablets	\$40	\$3.30	\$0.055		✓ ²		
d4T (6mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$55	\$2.30	\$0.038		✓ ^{1,2}		
d4T (12mg) + 3TC (60mg) + NVP (100mg)	HDPE bottle 60 tablets	\$52	\$4.30	\$0.072		✓ ^{1,2}		
EFV (50mg)	HDPE bottle 30 tablets	\$27	\$2.24	\$0.075	✓ ²		✓ ²	
EFV (200mg)	HDPE bottle 90 capsules	\$43	\$10.75	\$0.119	✓ ²	✓ ²	✓ ²	
EFV (200mg)	HDPE bottle 90 scored tablets	\$43	\$10.75	\$0.119				✓ ^{1,2}
LPV/r (100/25mg)	HDPE bottle 120 tablets	\$220	\$18.33	\$0.153			✓ ¹	
NVP (50mg/5ml)	HDPE bottle 240ml	\$53	\$1.75	\$0.007	✓ ^{1,2}	✓ ¹		



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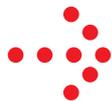
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ABBREVIATIONS

3TC: lamivudine; nucleoside analogue reverse transcriptase inhibitor.

ABC: abacavir; nucleoside analogue reverse transcriptase inhibitor.

AIDS: Acquired Immune Deficiency Syndrome.

ALP: AIDS Law Project.

ANVISA: Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil).

API: active pharmaceutical ingredient.

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

ARV: Antiretroviral.

ATV: atazanavir, protease inhibitor.

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

BI: Boehringer Ingelheim.

BMS: Bristol-Myers Squibb.

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

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

CCR5: chemokine coreceptor 5.

CF: Clinton Foundation.

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

CHF: Swiss franc.

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

DDU: 'Delivered duty unpaid'. A commercial term (incoterm) meaning that the seller delivers the goods to the buyer, not cleared for import, and not unloaded from any arriving means of transport at the named place of destination. The seller has to bear the costs and risks

involved in shipping the goods, other than, where applicable, any 'duty' (which includes the responsibility for the risks of the carrying out of the customs formalities, and the payment of formalities, customs duties, taxes and other charges) for import in the country of destination. Such 'duty' has to be borne by the buyer as well as any costs and risks caused by his failure to clear the goods for the import time.

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 16th Updated List was published in March 2009 and includes 14 antiretrovirals and five fixed-dose combinations.

EU: European Union.

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

FDA: United States Food and Drug Administration.

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

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

MVC: maraviroc; entry inhibitor.

NDRA: National Drug Regulatory Authority.

NFV: nelfinavir; protease inhibitor.

NGO: Non-Governmental Organisation.

NIH: National Institutes of Health.

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor.

NRTI: Nucleoside Analogue Reverse Transcriptase Inhibitor.

NtRTI: Nucleotide Reverse Transcriptase Inhibitor.

NVP: nevirapine; non-nucleoside analogue reverse transcriptase inhibitor.

OAPI: Organisation Africaine de la Propriété Intellectuelle (African Intellectual Property Organisation). Member states include 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.

PLHA: People Living With HIV/AIDS.

PMTCT: Prevention of Mother-to-Child Transmission.

ppy: per patient per year.

r: low-dose ritonavir, used as a booster.

R&D: Research and Development.

RAL: raltegravir; integrase inhibitor.

RTV: ritonavir; protease inhibitor.

SQV: saquinavir; protease inhibitor.

TAC: Treatment Action Campaign.

TB: tuberculosis.

TDF: tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

TPV: tipranavir; protease inhibitor.

TRIPS: Trade-related Aspects of Intellectual Property Rights.

UN: United Nations.

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

UNDP: United Nations Development Programme.

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

US FDA: United States Food and Drug Administration.

VL: voluntary licence.

WHO: World Health Organization.

WHO 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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