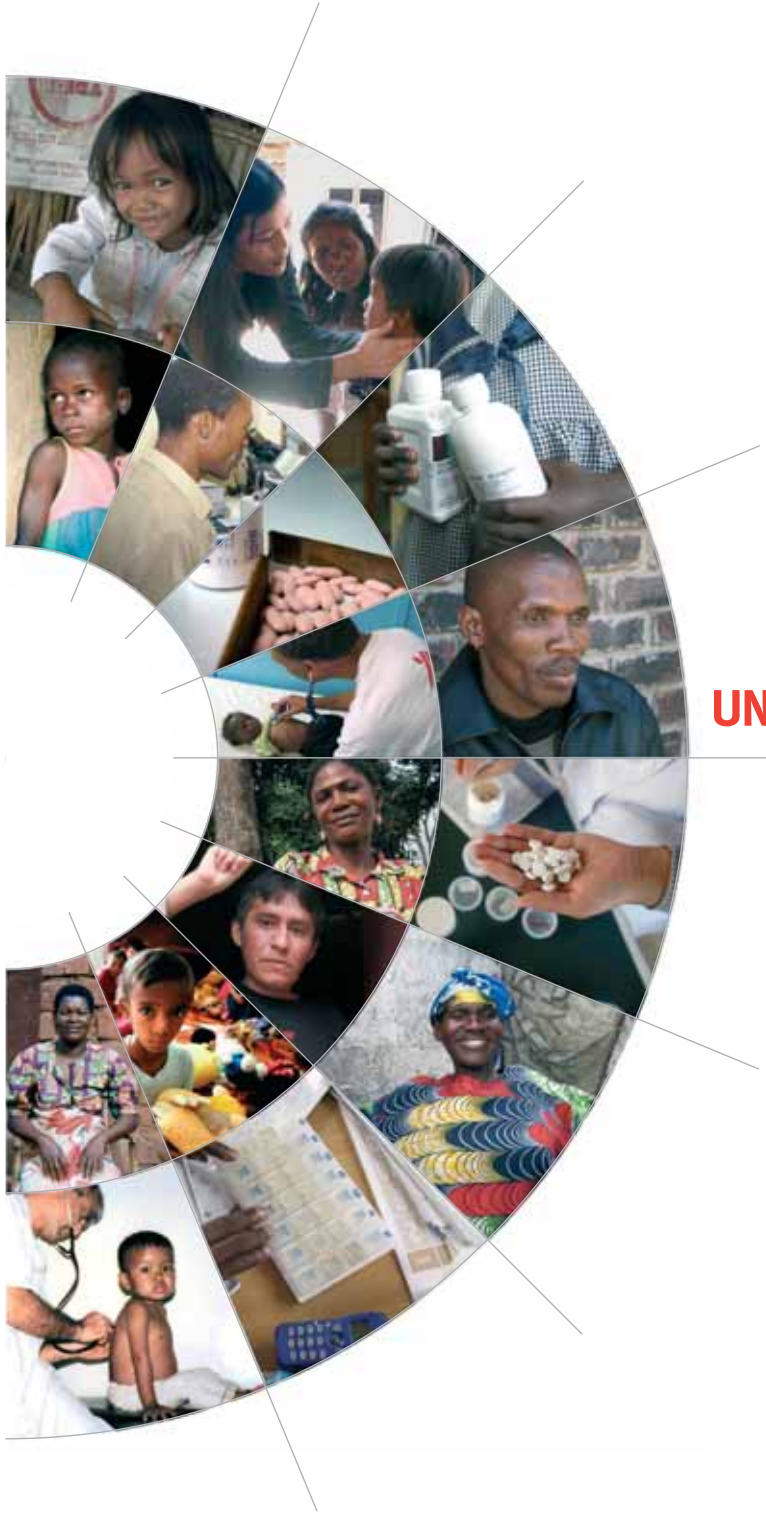

UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS

11th EDITION

JULY 2008

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDICINS SANS FRONTIERES

Disclaimer: 'Untangling the Web of Antiretroviral Price Reductions' is a pricing guide and cannot be regarded as a company price list. It is crucial that any purchaser verify prices and availability as well as quality status directly with the supplier before procurement. Médecins Sans Frontières has made every effort to ensure the accuracy of prices and other information presented in this report, but MSF makes no representations or warranties, either expressed or implied, as to their accuracy, completeness or fitness for a particular purpose. Inclusion of a product in this document does not indicate MSF purchases or uses the product. Information on patent status of the products mentioned in this guide is indicative only and not exhaustive, and should be verified with relevant national patent offices when used for other than reasons of general information.

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BACKGROUND

An estimated 33.2[1] million people are living with HIV/AIDS today around the world. 95% live in developing countries, yet only around one third[5,6] of the ten million people in need of antiretroviral treatment has access to it. There are many reasons for this, but accessibility and adaptability of antiretroviral drugs (ARVs) are critical factors.

Nearly ten years after antiretroviral therapy began in developing countries, Médecins Sans Frontières (MSF, or Doctors Without Borders) and other treatment providers continue to struggle with accessibility and adaptability of ARVs. While fierce competition among generic manufacturers helped bring prices for the first generation of ARVs down by more than 99% since 2000 (see graph 1), newer drugs are relatively expensive due to increased patenting in developing countries with generic production capacity and slow initial demand for newer drugs. In a changing access environment, new ways to keep AIDS medicines affordable must be set in motion both in order to give people already on ARVs the medical options to ensure survival, and also to keep improving the scale-up of access to ARVs for those not yet on treatment.

Accessibility is not simply a question of the price of the drugs. Access to ARVs can also be restricted by a lack of registration, patents and by problems due to the adaptability of different drugs to widely varying climatic or technological environments.

It is also becoming clear that the availability of newer drugs is severely curtailed because they are not always being developed with the needs of

Box 1: Quality Issues

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

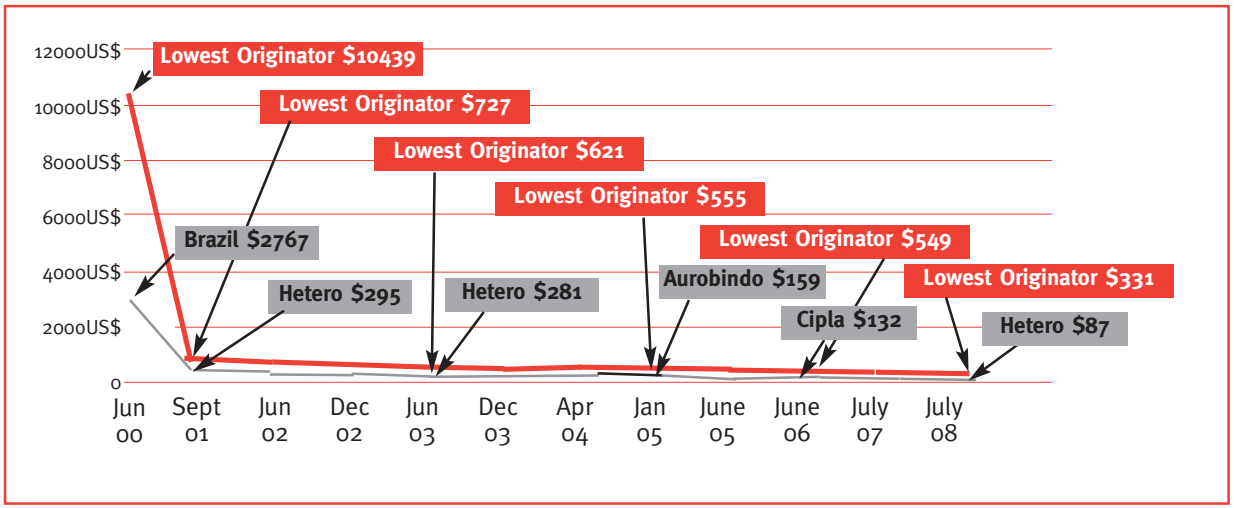
Readers and purchasers wishing to obtain more information about drug quality are therefore encouraged to consult the WHO list of Prequalified Medicinal Products which contains the products that "*meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis.*" More commonly known as the WHO prequalification list, the project was initiated by the World Health Organization (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. 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 last edition of the WHO prequalification list (Revised 63rd edition, 14 May 2008) appear in bold in the tables.

Please consult the WHO website (http://healthtech.who.int/pq/default.htm) for the latest list of prequalified products and for information on the status of dossier assessment.

Photo © Francesco Zizola/Noor

Graph 1: Competition as a catalyst for price reductions.
The fall in the price of first-line combination of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), since the first edition of Untangling the Web of Price Reductions.



people in developing countries in mind. This means newer drugs are not practical to use in resource-poor settings and for people with specific needs, notably pregnant women, children, and people who are co-infected with other diseases, such as malaria and tuberculosis (TB). It is critical that the drug development process systematically addresses developing country needs, to ensure that the majority of people living with HIV/AIDS across the globe are equally able to benefit from medical innovations.

MSF first published *Untangling the Web of Antiretroviral Price Reductions* as a pricing guide for the purchase of ARVs for developing countries, in October 2001. The lack of transparent and reliable information regarding prices of ARVs on the international market is an important factor that continues to hamper access to essential medicines in developing countries. The purpose of this document is to provide information on prices and suppliers that will help purchasers make informed decisions when buying ARVs. However, it is of course important to not only consider price when making purchase decisions; the quality assurance of the product should also be taken into consideration (see box 1).

NEW DRUG CLASSES BRING NEW OPPORTUNITIES, BUT COME WITH NEW BARRIERS

Adaptability Issues:

Over the last two 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. This report includes the newer drugs for which some pricing information was available (although many do not yet have any price information). 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, clinical trials for these drugs are designed to meet the requirements for registration in these countries. Data relevant to address the specific needs of populations in developing countries is therefore not obtained. For example, some of these new drugs have monitoring requirements that make their use impractical, or they lack data essential for target populations, such as pregnant women or people who need to take drugs for tuberculosis due to co-infection. A further example is the lack of knowledge about the interactions between antimalarials and antiretrovirals,[2] even though 80% of HIV-infected individuals live in regions where malaria is endemic.[3]

"There are still so many challenges and we don't really know who will tackle them, we lack paediatric drugs, and drugs that can be used during breastfeeding. We need certain drugs to be heat-stable, since many places don't have access to refrigeration. We need more fixed-dose combination options; for second-line treatment, for babies, as a once-a-day pill for pregnant women."
Dr. Alexandra Calmy, HIV Advisor to MSF's Access Campaign

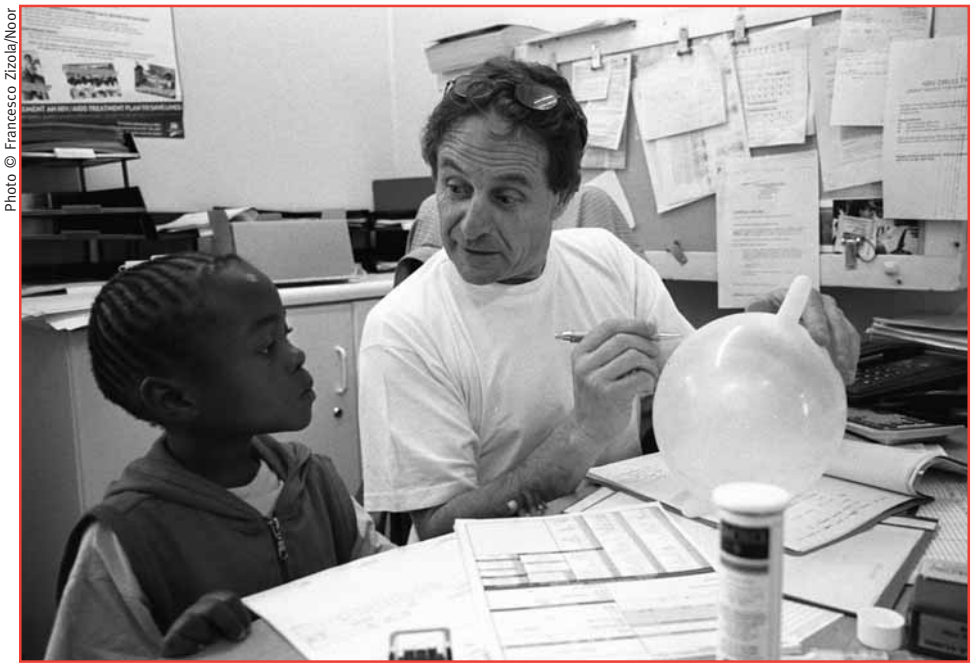


Photo © Francesco Zizola/Noor

Yet again, there is currently no safety and efficacy data for children for the new drugs darunavir, etravirine, maraviroc, tipranavir or raltegravir. 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 1997,[4] and the European Agency for the Evaluation of Medicinal Products (EMEA) followed suit in January 2007.[5] Globally, there were 420,000 estimated new cases of HIV infection in children in 2007, about 87% of which occurred in sub-Saharan Africa, and 0.001% in North America.[1,143] This is a clear illustration that prevention of mother-to-child transmission programmes in industrialised countries are working. The small number of cases in developed countries serves as a disincentive to pharmaceutical companies to invest in paediatric formulations (see box 2).

The need for high-tech monitoring can also affect the availability of antiretrovirals. For instance, the entry inhibitor maraviroc requires the HIV virus to have the chemokine coreceptor 5 (CCR5) in order to be effective. To identify whether a patient has CCR5 requires a complicated diagnostic test costing more than US$1,900 – a factor making its use unaffordable in developing country contexts, where even simple laboratory monitoring is rarely available.

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

> *"As a doctor, I need to know that when new products are developed that could really make a difference in my patients' lives, they will be affordable."*
> **Dr. Liesbet Ohler, MSF, Mathare, Kenya**

Accessibility Issues:

The majority of people living with HIV/AIDS in developing countries are still on their first combination of ARVs. However, this will begin to change dramatically over the next several years as patients develop resistance to their treatment, the need for access to newer treatments will become increasingly acute.

Newer medicines, however, still remain considerably more expensive than the first generation of ARVs, are increasingly patent-protected in countries with manufacturing capacity, or are not registered by pharmaceutical companies in developing countries. Raltegravir, as the first compound of the integrase inhibitor class, appears to be promising for use in developing countries due to the lack of drug interactions, and it has shown to be active in vitro against virus strains resistant to all existent ARV drug classes. It gained regulatory approval by the U.S. FDA in October 2007. However, its manufacturer, Merck, has neither indicated when the drug would be made available in developing countries, nor at what price.

The fusion inhibitor enfuvirtide is used as salvage therapy for patients who have exhausted all other treatment options, and has been on the market in the U.S. and Europe since 2003. However, its manufacturer, Roche, has stated that there will be no reduced pricing for the drug for developing countries now or in the future. Although the drug is complex to administer, requiring multiple daily injections, it could be a crucial option for certain patients. But Roche has defaulted to the pricing system that held sway before 2000, namely: one drug, one global price. This ignores the fact that extremely few people in developing countries would be able to access the drug at its current price: in

developed countries, enfuvirtide costs over US$25,000 per patient per year.[6]

> *"We are seeing a major crisis looming for people living with HIV/AIDS in the developing world. As doctors, we are deeply concerned to avoid the situation of the late 1990s, when people faced a death sentence because they could not afford the life-saving medicines widely available in rich countries."*
> **Dr. Tido von Schoen-Angerer, Executive Director, MSF's Access Campaign**

Three of the newer drugs, etravirine (NNRTI), maraviroc (entry inhibitor) and raltegravir (integrase inhibitor), have already been patented in India, which has been a key producer of affordable generic medicines because the country did not begin granting pharmaceutical patents until 2005. The impact of these patents on developing country access is likely to be considerable. Indeed, affordable ARVs manufactured in India have played a major role in 2007 in treatment scale-up across the developing world. For example, MSF in 2007 procured 85% of the ARVs it uses in its projects from Indian sources.

Now, however, the patenting of newer medicines in India means that generic manufacturers are unlikely to be able to enter the market and create the kind of competition that leads to the dramatic price reductions seen in the past. This in turn leaves access to these drugs in the hands of the monopoly producers that are free to set prices as they wish. Experience has shown that monopoly control also delays the entry of a drug into a particular market, with originator companies often slow to prioritise filing for drug registration in developing countries.

THE GROWING NEED FOR NEWER ARVs & THE CHANGING ACCESS ENVIRONMENT

> *"Affordable generic AIDS medicines have been one of the cornerstones of our ability to keep people alive."*
> **Dr. Selina Lo, Medical Coordinator, MSF's Access Campaign**

HIV/AIDS is a life-long disease requiring continuous access to different and newer medicine combinations for patients who develop resistance and side effects over time. As some patients in developing countries have now been on treatment for eight years or more, rates of resistance are growing and will continue to do so – this means that patients will need

Box 2: Children continue to be left behind

Because of the low numbers of children infected with HIV in developed countries, the development of paediatric ARV formulations is not a priority for pharmaceutical companies. However, it must be stressed that if prevention of mother-to-child transmission could be implemented more successfully in the developing world, through simplified and efficient strategies, there would be a dramatic reduction of child infections. Such strategies include the provision of triple ARV therapy to all HIV-positive pregnant women, and introducing ways to protect the child throughout the breastfeeding period.[7] This would lessen the need for paediatric treatment, as has been the case in wealthy countries.

But considering there are still large numbers of infants being infected in developing countries, treatment options are critical. There finally are several available paediatric fixed-dose combination (FDC) tablets that come in doses for various child sizes (the first WHO prequalified paediatric FDC was available a full six years after the adult one). Of the 22 ARVs approved by the U.S. FDA for adults, eight are not approved for use in children, and nine do not have any paediatric formulations.[8] The majority of these paediatric formulations continue to be ill-adapted for use in resource-poor settings. This means they either come in powder or syrup form, with some formulations having the drawbacks of bitter taste, and 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, or those who have been exposed to the NNRTI drug class through their mothers. However, this justified recommendation means taking a regimen including LPV/r syrup, which is nearly 70% more expensive than a liquid nevirapine-based regimen, and also requires refrigeration. There is thus an urgent need for the development of child-friendly doses of heat-stable protease inhibitors.

access to newer affordable medicines for the duration of their lives. In MSF's longest-running AIDS project in Khayelitsha, South Africa, approximately 22% of patients on treatment for five years needed to be switched to a second-line drug combination.

Fierce competition among multiple generic manufacturers in key producing countries like India helped bring prices down from US$10,000 per patient per year in 2000 to less than US$90 today for the most commonly-used first-line drug combination in the developing world (see graph 1). Production by multiple manufacturers was only possible due to the lack of patents in countries like India. Additionally, this allowed the production of fixed-dose combination 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 tomorrow's battle for access to affordable ARVs will need to be fought in a different way. It will require routine use of public health safeguards in patent laws, and of flexibilities in the World Trade Organization's (WTO) TRIPS Agreement (Trade-related Aspects of Intellectual Property Rights), such as compulsory licensing. Increased global patenting through TRIPS is systematically reducing possibilities of producing generics, thereby changing the rules of the game and keeping prices high for the newer medicines people need (see graph 2). This puts a serious strain on, and threatens the sustainability of, national AIDS treatment programmes that are already struggling to implement and scale-up treatment.

Under the TRIPS Agreement and the Doha Declaration on TRIPS and Public Health, agreed by WTO member states in 2001, least-developed countries (LDCs) are not required to grant or enforce patents on pharmaceuticals until 2016 (patents on pharmaceuticals have been granted in many LDCs, but these countries are not obliged to enforce them, due to the 2016 extension). Other countries, such as the key manufacturing countries India and Brazil, were obliged to introduce patent protection for pharmaceuticals as of 2005, thereby restricting competition and fostering monopoly control.

While most companies today do offer discounts through tiered pricing, experience has shown that in the absence of competitors, manufacturers enjoying a monopolistic situation do not reduce prices deeply enough to make medicines affordable for developing countries. Also, countries that are classified as 'middle-income,' such as Brazil, Thailand, China or Guatemala, are often are 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 overridden through compulsory licensing is what makes companies respond and reduce prices.

Flexible Patent Laws

The Doha Declaration stresses that countries have the right to design patent laws that serve the interest of public health. India made use of this when amending its patent law, which came into force in 2005. The law has strict criteria as to which compounds deserve a patent and which do not (see box 3), and also allows any interested party – whether within India or not – to oppose a patent before or after it is granted ('pre-grant' and 'post-grant oppositions'). Such oppositions have been filed in India by Indian and Brazilian civil society groups, which both depend on India remaining a source of affordable medicines (see box 4).

Yet despite these safeguards, it is likely that many of the newest ARVs will be patentable under India's law, and several already have been (etravirine, maraviroc, raltegravir). Only through licensing, be it voluntary or compulsory, will generic competition be able to occur.

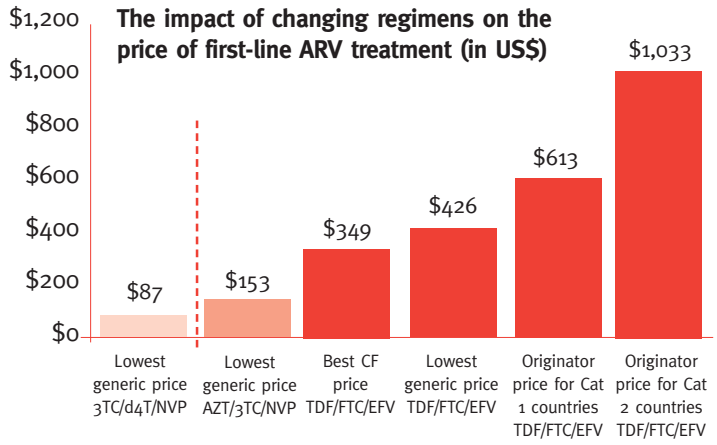
Often the mere prospect of patents being granted for specific drugs in India discourages generic manufacturers from making an investment and entering the market, as companies fear being shut out of the market if a patent were subsequently to be granted. This means that several drugs that have been available for use in developed countries for five years or more, but whose patents are awaiting review by the Indian Patent Office, remain relatively expensive, because not enough competition has taken place to bring prices down.

Keeping the Door Open for Competition, Despite Patents

When drugs *are* patented, the only way to overcome monopoly control and keep the door open for competition is either through compulsory licensing or voluntary licensing. 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 that is limiting access, by giving another entity a licence to produce the drug.



Graph 2: In 2006, WHO published the revised *Antiretroviral therapy for HIV infection in adults and adolescents* guidelines, recommending that patients start to move away from stavudine (d4T)-based first-lines to less toxic regimens based on either zidovudine (AZT) or tenofovir disoproxyl fumarate (TDF).[15] Changing a patient's treatment regimen from the most affordable first-line ARV combination to these less toxic options involves, at best, almost doubling the price for an AZT-based FDC. For a TDF-based regimen, the increase is even more dramatic, ranging from fourfold to over elevenfold in some middle-income countries that are not be able to access the generic products because of patent protection.

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 lopinavir/ritonavir (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 US$2,200 per patient per year to US$898 in Thailand and US$550 in countries in the Clinton Foundation Consortium.

Similarly, a CL issued by Brazil for efavirenz in April 2007 brought the cost for the drug in Brazil down by almost 70%, from US$576 to US$190 per patient per year. In the few months after importing the cheaper generic, until the end of 2007, the Brazilian government saved US$30 million, with a further US$237 million of savings projected by 2012 - savings that can be expected to contribute to the sustainability of the Brazilian universal AIDS treatment programme. Issuing a CL can be expected to have additional knock-on benefits in terms of reducing the price of other drugs, as companies may prove to be more willing to negotiate price reductions in the future, now that the precedent of issuing a CL has been set.

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 helping ensure

Box 3: Limiting patents to innovations

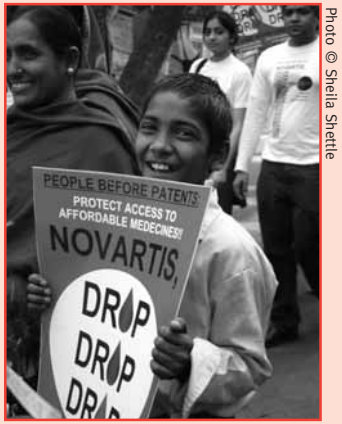


Photo © Sheila Shettle

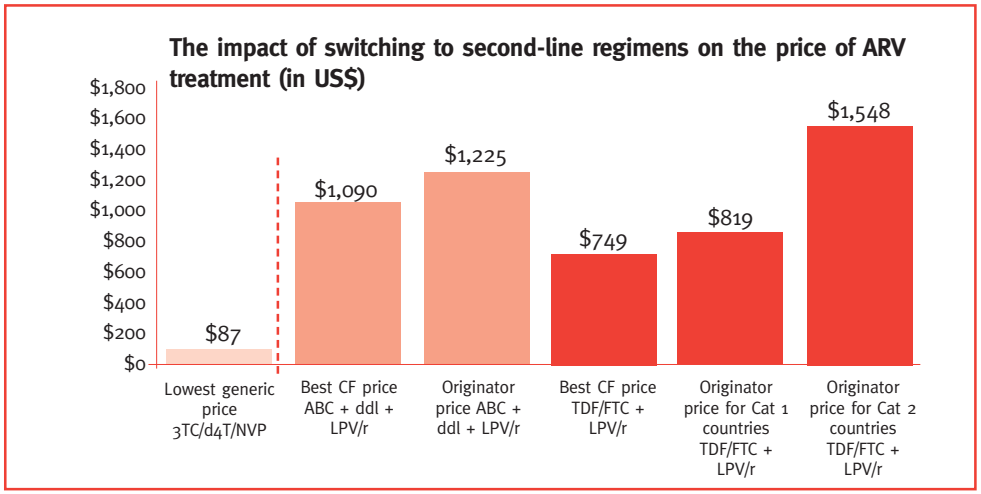
India's Patents Act, which came into effect in 2005, does not allow patents to be granted for compounds that were invented prior to 1995. It also contains a provision that states that a compound should only be patentable if it shows improved efficacy over previously-existing compounds (section 3d). This is aimed at limiting the ability of pharmaceutical companies to apply for patents on previously-known compounds and extend patents artificially, by repeatedly applying for new patents based on minor changes to drug formulations that do not represent innovations - a process called 'evergreening.' Section 3d of India's Patents Act is often the basis for pre-grant oppositions.

In 2006, Swiss pharmaceutical company Novartis did not receive a patent for a specific form of its cancer drug imatinib mesylate (marketed as Gleevec) based on section 3d of India's Patents Act. The company took the Indian government to court that same year, contesting not only the rejection of its patent, but also the provision in the law itself that was the grounds for the patent being rejected. A global mobilisation among civil society led to nearly half a million people voicing their concerns with the company's actions through an international petition campaign. In August 2007, Novartis lost its case in the Indian court, which upheld the law.

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.

Voluntary Licensing:

When a drug is patented in a given country, the patent holder may choose to issue 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 to merely extend the originator company's control over a given market, stipulating aspects such as which source the active ingredient must be purchased from, as well as to which countries the drugs can be exported (see box 5). Such restrictive VLs ultimately do not lead to the unhindered competition that allows patients to benefit from the lowest prices possible.



Graph 3: In 2007, WHO published the report *Prioritising second-line antiretroviral drugs for adults and adolescents*,[57] simplifying the recommendations for second-line ARV treatment to lopinavir/ritonavir (LPV/r) with either abacavir (ABC) and didanosine (ddI), or TDF and lamivudine (3TC).* Changing a patient's regimen because of the emergence of resistance from the most affordable first-line combination today to either of these recommended second-line regimens will at best increase the price of treatment nine-fold. In some instances, the price hike could be as much as 17-fold in some middle-income countries that are not able to access the generic products because of patent protection.

**WHO guidelines state: "emtricitabine (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 and has the same resistance profile".*

Box 4: The first successful patent opposition in India

In May 2006, the Indian Network of People Living with HIV/AIDS (INP+) and the Positive Women's Network (PWN) filed a pre-grant opposition against the patent application filed by German pharmaceutical company Boehringer Ingelheim for the syrup paediatric formulation of nevirapine. In June 2008, the Indian Patent Office rejected Boehringer's patent. This is the first decision by India's Patent Office that pertains to the 13 pre-grant oppositions filed by Indian civil society against HIV/AIDS drug patents since 2006, and sets an important precedent for those to follow.

"We're running into a wall when it comes to future AIDS regimes. Newer drugs will now be patented in places like India, where in 2007 we sourced over 80% of our ARVs, as affordable generics. India has only been able to make these generics because the drugs were not patented there. But this is changing, and our sources of affordable medicines is drying up."
Dr. Alexandra Calmy, HIV advisor to MSF's Access Campaign

Patent Pooling:

Dealing with existing patents can be done on a case-by-case basis through voluntary or non-voluntary licensing. But it is also possible to have a collective management of intellectual property through patent pooling. A patent pool is created when a number of patent rights, held by different owners, are brought together, or pooled, and collectively managed. The pooling of patents can be a useful strategy to ensure there are multiple producers, and to overcome barriers to the development of fixed-dose combinations (which is often restricted due to patents on the individual compounds) or specific formulations. The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property[9] recommends exploring the feasibility of such patent pools. In July 2008, UNITAID's Executive Board supported the principle of establishing a patent pool of medicines.[144]

Box 5: Voluntary licences: the Devil is in the Details

U.S. pharmaceutical company Gilead Sciences has applied for patents in India for tenofovir disopoxil fumarate (TDF), but the applications are still under review by the Indian Patent Office. In May and September 2006, Indian civil society organisations 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.

Shortly after the first opposition was filed, Gilead offered voluntary licence agreements to any interested generic manufacturer in India. These VLs are restrictive, in that they, for example, stipulate that the manufacturers must purchase the active pharmaceutical ingredient (API) 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, such as Brazil and China. This means that while competition among multiple manufacturers (licensees) within India is taking place, Gilead maintains control over which countries are able to benefit from these lower prices, often keeping itself as the monopoly source in these countries.

It is somewhat surprising that these VLs were pursued, especially considering that it remains unclear whether Gilead will be granted a patent for TDF at all. If Gilead's patent in India is rejected, generic companies will hopefully be able to produce the drug freely, without any of the constraints of the licence.

CONCLUSION

Nearly one decade since antiretroviral treatment began in developing countries, a new set of challenges has emerged with regard to accessing the medicines needed to sustain life-long treatment for the millions of people who need it.

One challenge lies in the fact that many of the therapeutic advances in HIV/AIDS are not being developed in a way that makes them most useful to 95% of those infected with HIV across the globe. This means that there must be a concerted effort to ensure that developing country needs are taken into account in the AIDS medicine research and development process. This will require changing the system, as all too often, conducting this research is not in the interest of market-driven originator companies.

A second challenge lies in the fact that increased global patenting - particularly in key generics manufacturing countries such as India and Brazil, but also in Africa - will mean that AIDS medicine prices are not likely to drop as dramatically as they did from 2000 until today (by 99%). It will take routine use of flexibilities in the TRIPS Agreement by affected countries, voluntary licences with no strings attached, and new mechanisms such as patent pools to ensure ongoing access for those in need.

Civil society pressure has been a critical factor throughout the duration of the battle for access to AIDS treatment over the past decade. Through the process of opposing patents and supporting countries in their right to provide their people with affordable medicines, civil society engagement will continue to be indispensable.

METHODOLOGY

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 27 June 2008.

All originator companies marketing ARVs were included in the survey. But the list of generic producers is by no means exhaustive.[10] Only generic companies that have at least one ARV listed on the WHO prequalification list on the date of the initial request for information were included in this publication. The initial questionnaires were sent in the middle of April 2008.

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, Emcure and Apotex 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 consult the most recent edition of the World Health Organization's publication, "Sources and prices of selected drugs and diagnostics for people living with HIV/AIDS."[11]

- 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).[12] These trade terms outline the responsibilities of the manufacturer and purchasers with regard to transport, international freight and insurance costs. Further explanations of these terms are included in the annexes. Prices in the publication have not been adjusted to incorporate the different terms. The U.S. General Accountability Office has recently demonstrated that these differences do not undermine their essential comparability.[13]

- Originator and some generic companies have different eligibility criteria for differential pricing for countries and entities. The different categories of prices are detailed in the product cards. More detailed information on the different eligibility criteria is provided in the annexes.

- The Clinton HIV/AIDS 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 over 40 different ARV formulations, both paediatric and adult. The current price list is included in Annex 13.[14]

- 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 pre-qualification list is updated regularly, the list should be consulted for up-to-date information regarding quality. http://healthtech.who.int/pq/default.htm

Photo © Mariella Furrer

How to read the product cards?

General information
General information on the history of the product and relevant WHO guidance is provided for each of the antiretrovirals (ARVs) included in this publication.[15,16] Separate cards are included for both single ARVs and fixed-dose combinations (FDCs) containing two or three ARVs.

Prices quoted by companies for eligible developing countries
All prices are quoted in United States Dollars (US$). Conversions were made on the day the price information was received using the currency converter site www.oanda.com. Prices are rounded up to the third decimal for unit price and to the nearest whole number for yearly price per patient.

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

For paediatric treatments, prices are calculated for a 10kg child using recommended dosing based on weight bands, as it appears in the WHO treatment guidelines.[16] This is an estimate, as the weight of a child increases during any given year. When it was not possible to calculate the dose for a 10kg child, only the unit price is indicated. For paediatric FDCs the dosages used for the calculation is as recommended by the Paediatric Antiretroviral Working Group at WHO.[17]

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

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

The Clinton Foundation negotiates with several manufacturers for reduced prices for over 40 different ARV formulations for countries in their pooled procurement consortium. Manufacturers who have a product included in the most recent price announcement are indicated by a (CF) in the header of the table. Further details of the specifics of the product can be found in Annex 13.[14]

WHO Prequalification Project
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. Products included in the most recent edition of the WHO list of Prequalified Medicinal Products for Antiretrovirals (last update 14 May 2008) are in **BOLD** in the table. Readers and purchasers wishing to obtain more information about the quality of ARVs are encouraged to consult the WHO Prequalification Project website as this list is updated regularly. (http://healthtech.who.int/pq/default.htm)

Evolution of the lowest price quoted by companies for eligible countries since 2001
This chart shows the price evolution over time, for both originator and generic products, as quoted to MSF for this document since 2001. If a WHO prequalified generic product is available, the lowest price quoted is shown in the graph. If no generic product is WHO prequalified, the lowest possible price quoted is featured in the graph.

Spotlight on access issues
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. A special comment has been included when appropriate with regard to paediatrics.

MARAVIROC (MVC)

ENTRY INHIBITOR

General information

- Therapeutic class: chemokine coreceptor 5 (CCR5) antagonist.
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced adult patients infected with only CCR5 tropic HIV-1, evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.[18]
- Originator company and product name: Pfizer, Selzentry.
- First approved by the U.S. Food and Drug Administration (FDA) on 7 August 2007.[19]
- Not included in the WHO Model List of Essential Medicines (EML).[20]
- Basic patent was applied for by Pfizer in December 1999[21] and is due to expire in 2019. In May 2001, Pfizer applied for an additional patent more specifically related to crystalline maraviroc.[22]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Maraviroc is classed as a CCR5 coreceptor antagonist that targets the penetration of cells by the HIV virus. This drug option is predominately used in the developed world for '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 coreceptor. The recommendation is for patients to have a tropism test to look for this coreceptor prior to treatment. Today, this test is not widely available and it is expensive at approximately US$1900.[23] In developing countries, where basic laboratory monitoring is not always available, the reality of this type of testing being available is limited.

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

Patents: Pfizer obtained a patent in India in October 2007.[24] This patent may block manufacture of generic formulations of maraviroc in India, limiting the much-needed competition that historically has been shown to lead to price reductions.

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

ENFUVIRTIDE

FUSION INHIBITOR

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.[25]
- Originator company and product name: Roche Laboratories and Trimeris, Fuzeon.
- First approved by the U.S. Food and Drug Administration (FDA) in March 2003.[19]
- Not included in the WHO Model List of Essential Medicines (EML).[20]
- Basic patent on enfuvirtide applied for by Duke University in June 1994[26] and 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,[27] 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.[28] In November 2007, Novartis Vaccines and Diagnostics, Inc. filed a suit against Roche and Trimeris, alleging infringement of Novartis' patent.[29]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Enfuvirtide was the first drug of the new fusion inhibitor class to be approved. The novel mechanism of action targets 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.

This drug 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 and discard the balance. This is not adapted for use in resource-limited settings, and the current price in the developed world of over US$25,000 per patient year is prohibitive for many developing countries that may have a need for this product.[6]

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

Paediatrics: The drug is approved for use in children over six.

RALTEGRAVIR (RAL)

General information

- Therapeutic class: integrase inhibitor.
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.[30]
- Originator company and product name: Merck & Co., Isentress.
- First approved by the U.S. Food and Drug Administration (FDA) on 12 October 2007.
- Not included in the WHO Model List of Essential Medicines (EML).
- Basic patent applied for in October 2002 by the Institute for Research in Molecular Biology (IRBM), Pomezia, Italy, one of Merck's research sites.[31] Patent due to expire in 2022. In 2005, Merck and IRBM applied for another patent on the potassium salt of RAL.[32]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Raltegravir (RAL) is the first of a new class of drugs (integrase inhibitors), which have a novel mechanism of action and no apparent cross-resistance with other ARVs. RAL, unlike 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.

Merck was invited to contribute a price for this publication and has indicated that RAL is not yet commercially available in the developing world and prices have not been set for these countries. Merck did provide information that they plan a differential pricing structure and have designated which countries will be eligible for these prices when released. Merck reported RAL is today approved in more than 30 countries and the company plans to file for registration in more than 100 countries, including all those in which patients participated in clinical trials.

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 2007.[33] Generic competition to reduce the price of the medicine will therefore only be possible under voluntary licences from the patent holder or compulsory licences issued by the government.

Paediatrics: The safety and efficacy of RAL in patients under 16 year of age have not been established.

EFAVIRENZ (EFV)

General information

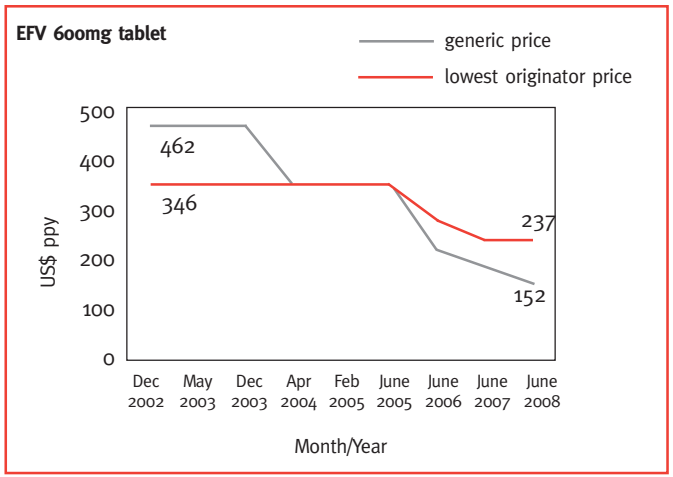
- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Indicated for first- and second-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Originator companies and product brand names: Bristol-Myers Squibb (BMS), Sustiva, or Merck, Stocrin.
- First approval by U.S. Food and Drug Administration (FDA): 17 September 1998.[19]
- Included in the 15th edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2007: US$956 million; 2006: US$791 million; 2005: US$680 million; 2004: US$621 million; and 2003: US$544 million.[34,35,36]
- The basic patent on EFV was filed in 1993 by Merck, and is due to expire in 2013.[37]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Merck		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides (CF)
		Category 1	Category 2						
Eligibility restrictions		See Annex 10		None	None	None	None	None	None
EFV 50mg capsule	--	**(0.120)**	**(0.210)**	**(0.092)**					
EFV 50mg tablet	--	**(0.120)**	**(0.210)**						
EFV 100mg capsule	--			**(0.483)**					
EFV 200mg capsule	3	**394 (0.360)**	**821 (0.750)**	**183 (0.167)**	186 (0.170)	153 (0.140)		**210 (0.192)**	186 (0.170)
EFV 200mg tablet	3	**394 (0.360)**	**821 (0.750)**						
EFV 600mg tablet	1	**237 (0.650)**	**657 (1.800)**	**158 (0.432)**	**170 (0.467)**	146 (0.400)	**152 (0.417)**	**185 (0.506)**	**180 (0.500)**
EFV 30mg/ml suspension	--	**(0.094/ml)**	**(0.151/ml)**						

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest price quoted for eligible developing countries since 2002.

As of June 2008, there were five WHO prequalified generic sources of EFV 600mg and the lowest price product is shown here.

Since 2002, the originator price has decreased by 32% while the generic prices dropped by 67%.

Spotlight on access issues:

Efavirenz (EFV) is a key drug for first-line treatment, especially in patients co-infected with TB. There is an interaction between NVP and rifampicin, one of the main drugs for the treatment of TB, resulting in lower blood levels of NVP. EFV does not share the degree of this interaction and can be used as an alternative. The price, however, is restrictive especially to countries that belong to Merck's second pricing tier and where EFV on its own can then cost more than six times the cost of the most widely-used triple FDC (3TC/d4T/NVP). Merck plans to phase out the 200mg and 50mg capsule formulations that will be replaced by the tablets.

Patents: Despite generic competition from a number of Indian manufacturers, EFV remains expensive in countries where Merck holds patents that block the generic companies from offering their products for sale. Various initiatives by governments and civil society groups have been undertaken in some of these countries where EFV is patented, to ensure generic competition and more affordable 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$120 ppy, which is less than half the previous price of US$511 ppy.[38,39]

• In April 2007, Brazil, after numerous negotiations with Merck, issued a compulsory licence to import more affordable generic versions of EFV from India. The price of EFV in Brazil was US$576 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a generic prequalified by WHO at a cost of US$190 ppy.[40]

• 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 licence its product to other producers, opening the opportunity for generic competition in South Africa, which is expected to drive down the price of EFV in the country.[41]

• In India, a patent on a process for preparing form 1 of crystalline EFV was granted in June 2005.[42] Even though Merck does not hold a patent on EFV, as a product, this recently granted process patent appears to protect a key process for manufacturing EFV and could therefore have some 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 available to them under Indian patent law.[43] A decision of the patent office is pending.

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. This can be very confusing to explain to caregivers when changing to an oral dosage form.

ETRAVIRINE

NNRTI

General information

- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Not currently included in WHO guidelines.
- Approved by U.S. Food and Drug Administration (FDA) for treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents.[44]
- Originator company and product name: Tibotec Pharmaceuticals, Intelence.
- First approved by the U.S. FDA on 18 January 2008.[19]
- Not included in the WHO Model List of Essential Medicines (EML).
- The basic patent on etravirine was applied for by Janssen Pharmaceutica in 1999 and is due to expire in 2019.[45] Both Janssen Pharmaceutica and Tibotec are now part of Johnson & Johnson.[46,47]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Etravirine, was approved by U.S. FDA in January 2008 and in June 2008 received a conditional marketing authorization from the EMEA, but is not approved by any developing country health authority. We have asked Tibotec to provide a price for this product for inclusion in this publication, and they indicated that etravirine will be included in its "Global Access Program", however no price was provided by Tibotec.

Patents: Patents have been applied for widely in the developing world, including in Africa. In September 2006, Janssen Pharmaceutica was granted a patent in India.[48] This patent may block manufacture of generic formulations of etravirine, limiting the much needed competition that historically has been shown to catalyse price reductions.

Paediatrics: Etravirine is today not approved for use in children.

NEVIRAPINE (NVP)

General information

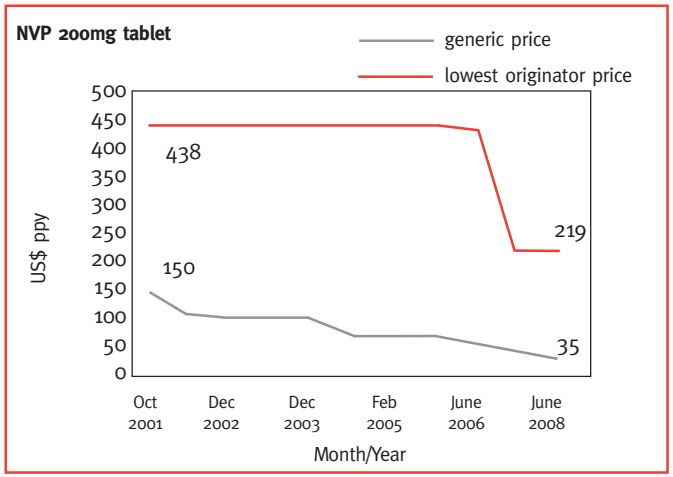
- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Indicated for first- and second-line, for adults, adolescents and children (WHO 2006 guidelines)[15,16]
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune.
- First approval by U.S. Food and Drug Administration (FDA): 21 June 1996.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2007: US$412 million; 2006: US$370 million; 2005: US$386 million; 2004: US$378 million.[49,50,51,52]
- The basic patent on NVP was applied for by BI in November 1990, and is due to expire in November 2010.[53]
- BI also applied for a patent on the hemihydrate form of NVP, used in the suspension in 1998, which is due to expire in 2018.[54]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Boehringer Ingelheim		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Huahai (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
		Category 1	Category 2							
Eligibility restrictions		See Annex 2		None	None	None	None	None	None	None
NVP 200mg tablet	2	**219 (0.300)**	**438 (0.600)**	**46 (0.063)**	**35 (0.048)**	**44 (0.060)**	**46 (0.063)**	52 (0.071)	**51 (0.070)**	**58 (0.080)**
NVP 10mg/ml suspension	20ml	**380 (0.052/ml)**	**533 (0.073/ml)**	**66 (0.009/ml)**	73 (0.010/ml)					
NVP 25mg granules	--									(2.500)
NVP 50mg granules	--									(3.000)

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were six WHO prequalified generic sources of NVP in this publication. The lowest available generic price is shown here. While it was a positive result that the originator dropped its price by 50% in 2007, the generic price has decreased by almost 80% over this period, and today is now roughly 16% of the originator price.

NEVIRAPINE (NVP)

NNRTI

Spotlight on access issues:

Nevirapine (NVP) is a widely-used ARV, predominately in first-line regimens. The price of NVP has decreased dramatically over the past years as a result of generic competition. It has been an important component of the fixed-dose combinations that have fostered treatment scale up in resource-limited settings.

Patents: BI did obtain 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 did not grant patents on medicines at the time. Many developing countries, where NVP is under patent, do 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 opposed the granting of this patent before the Indian patent office 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 constitutes an important victory for Indian civil society, as this is the first patent application related to a HIV medicine that has been rejected as a result of a pre-grant opposition.[55]

Paediatrics: NVP is approved for use and widely used in children. Generic manufacturers have been developing triple fixed-dose combinations including NVP, but today there is only one WHO prequalified triple FDC including NVP for children. To give a clinician flexibility in the prescribing of ARV regimens, there is a need for a single simple adapted formulation of NVP. The Paediatric Antiretroviral Working Group at WHO has given "urgent" priority to the development of a 50mg tablet. With the increased prevalence of HIV/TB co-infection, there is an additional need for further studies into the interactions between NVP and the TB drugs rifampicin and rifabutin in these young populations.[17]

BI has a donation program of NVP for the prevention of mother-to-child transmission. 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. Therefore, today it costs more to treat a 10kg child with NVP than an adult.

ABACAVIR (ABC)

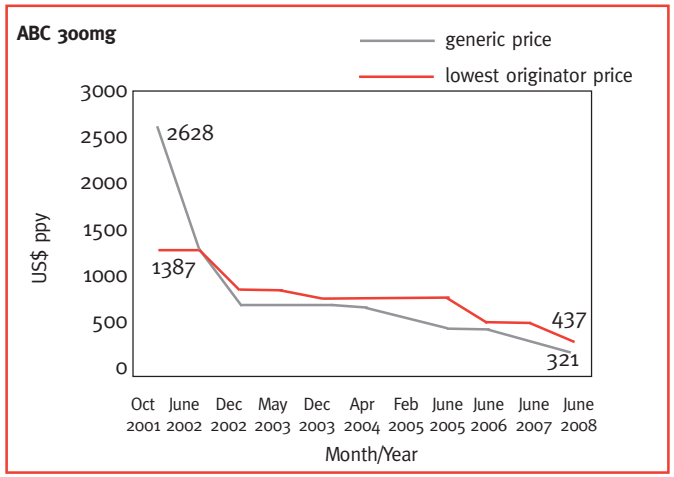
General information

- Therapeutic class nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Ziagen.
- First approval by U.S. Food and Drug Administration (FDA): 17 December 1998.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product for 2007: US$215 million; 2006: US$230 million; 2005: US$268 million; 2004: US$290 million.[58,59,60,61]
- The basic patents on ABC were applied for by GSK in 1989[62] and 1990,[63] and these are due to expire in 2009 and 2010, respectively. GSK subsequently applied for an additional patent on the hemisulfate salt of ABC in 1998,[64] and on compositions of ABC particularly relevant for paediatric use in 1999,[65] which are due to expire in 2018 and 2019, respectively.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy
Eligibility restrictions		See Annex 2	None	None	None	None	None
ABC 300mg tablet	2	**437 (0.599)**	**321 (0.440)**	**334 (0.458)**	336 (0.460)	**365 (0.500)**	473 (0.648)
ABC 20mg/ml oral solution	10ml	**230 (0.071/ml)**	**259 (0.071/ml)**	420 (0.115/ml)			
ABC 60mg tablet	4			160 (0.110)		194 (0.133)	

(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.
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were three WHO prequalified generic sources of ABC and the lowest-price product is shown here.

Since 2001, the originator price has decreased by 68%, while the generic price has decreased by 88%.

ABACAVIR (ABC)

NRTI

Spotlight on access issues:

In 2007, WHO convened a technical consultation to simplify the choice of second-line regimens. Abacavir (ABC), in combination with ddI, was one of the two recommended NRTI backbones (the second option being TDF/3TC) to be added to a boosted PI for patients whose initial first-line regimen was 3TC/d4T/NVP.[57]

ABC will continue to be an important second-line ARV for the developing world. The current price, however, is quite prohibitive with the ABC formulation alone costing between three and four times more than the most widely-used triple FDC first-line regimen (3TC/d4T/NVP). Additionally, GSK's differential pricing structure excludes non-African countries that are not funded by the Global Fund. This structure leaves these countries paying more than US$4,900 per patient year.[66]

Patents: As shown above, the price of ABC decreased significantly with the arrival of generic competition. This was 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, 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.[67] However, the patent more specifically related to paediatric formulations was granted in December 2007.[68] This recently granted 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. ABC does exist in a liquid formulation and generic manufacturers are starting to work on a low-dose paediatric tablet. 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 NVP, and the lack of dosage data on the EFV for children under three. The Paediatric Antiretroviral Working Group at WHO has given "urgent" priority to the development of a 60mg tablet. 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.[17]

DIDANOSINE (ddI)

General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for second-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- 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.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: In 2005: US$174 million; 2004: US$274 million; 2003: US$354 million. After 2005, there are no sales figures listed in the company's annual report.[36]
- Basic patent on ddI 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.

Price information: Prices in US$ quoted by companies for eligible developing countries

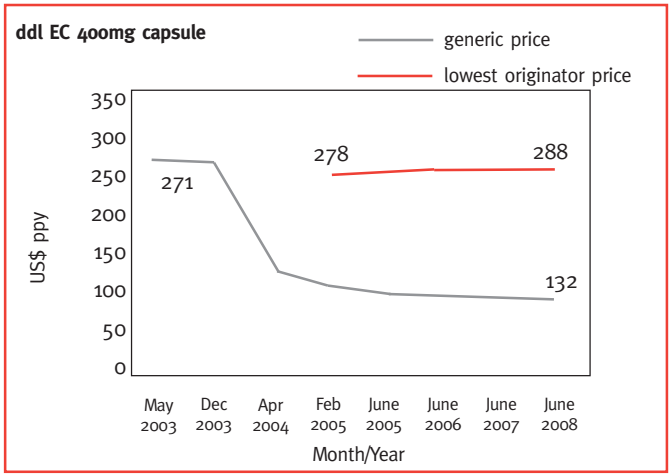
	Daily dose	Bristol-Myers Squibb		Aurobindo (CF)	Cipla	Hetero	Ranbaxy
		Category 1	Category 2				
Eligibility restrictions		See Annex 2		None	None	None	None
ddI 25g tablet	5	**212 (0.116)**	**429 (0.235)**		115 (0.063)		
ddI 50mg tablet	--	**(0.158)**	**(0.235)**		(0.079)		
ddI 100mg tablet	4	**310 (0.212)**	**364 (0.249)**	**219 (0.150)**	166 (0.114)	160 (0.110)	242 (0.166)
ddI 150mg tablet	--	**(0.308)**	**(0.345)**	**(0.225)**	(0.167)		
ddI 200mg tablet	--	**(0.425)**	**-**	**(0.300)**	(0.232)		
ddI 125mg enteric-coated capsule	--			(0.186)			
ddI 250mg enteric-coated capsule	1	**223 (0.611)**	**247 (0.667)**	172 (0.471)	103 (0.283)	139 (0.380)	170 (0.466)
ddI 400mg enteric-coated capsule	1	**288 (0.789)**	**319 (0.846)**	270 (0.740)	132 (0.363)	161 (0.440)	304 (0.832)
ddI 2g powder for reconstitution (Final concentration 10mg/ml)	12ml	**276 (12.590/2g)**	**305 (13.937/2g)**	**88 (4.000/2g)**			

(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.

Note: BMS second category pricing is provided in South African Rand. These were converted to US$ on the date the prices were received, and hence fluctuations in the US$ do impact these prices.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.

DIDANOSINE (ddI)



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

As of June 2008, there were no WHO prequalified generic sources of ddI 400mg enteric-coated capsules. The lowest available generic price is shown here.

Spotlight on access issues:

In 2007, WHO convened a technical consultation to simplify the choice of second-line regimens. Didanosine (ddI), in combination with abacavir (ABC), was one of the two recommended NRTI backbones (the second option being TDF + 3TC) to be added to a boosted PI for patients whose initial first-line regimen was 3TC/d4T/NVP.[57]

Didanosine will continue to be an important second-line ARV for the developing world. However, BMS's differential pricing structure limits access to these prices to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries paying more than US$3,800 per patient year for ddI enteric-coated (EC) 400mg capsules, which is prohibitive for many of these countries.[66]

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.

Today, we still do not have any generic versions of ddI EC prequalified by WHO.

Paediatrics: For younger children, the only options are buffered tablets that come with a high pill burden, or the ddI powder for reconstitution, which requires multiple dilutions, first with water and second with an antacid, to obtain the final concentration. Once reconstituted, the solution must be refrigerated and must be discarded after 30 days. The ddI EC 125mg, which is the best-adapted option for older children who can swallow, has no differential price. The price in the developed world, at more than US$1,000 per patient year, is prohibitive for the developing world.[66]

EMTRICITABINE (FTC)

General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first-line, for adults (WHO 2006 guidelines).[15]
- Originator company and product brand name: Gilead, Emtriva.
- First approval by U.S. Food and Drug Administration (FDA): July 2003.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2007: US$31.5 million; 2006: US$36.3 million; 2005: US$47.4 million; 2004: US$57.6 million.[69,70]
- The basic patent on 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.[71,72]
- Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.[73,74] These are due to expire between 2010 and 2012. In 2005, Gilead acquired the royalty interest for FTC under a US$525 million agreement with Emory University.[75]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Hetero
Eligibility restrictions		None
Emtricitabine 200mg tablet	1	66 (0.180)

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 TDF.

According to the WHO treatment guidelines, "*FTC is an equivalent alternative to 3TC as it is structurally related to 3TC, shares the same efficacy against HIV and Hepatitis B virus and has the same resistance profile.*"[15]

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.[76]

In mid 2006, Gilead signed licensing agreements with ten generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's products to a limited list of countries, against the payment of a 5% royalty.[77]

Paediatrics: FTC is approved for use in children and has the advantage of daily dosing. The paediatric formulation produced by Gilead is a solution that requires refrigeration prior to dispensing and must be used within three months, stored at temperatures below 25°C. This is not adapted to developing world needs. The Paediatric Antiretroviral Working Group at WHO has given "important" priority to the development of a 35mg tablet.[17]

LAMIVUDINE (3TC)

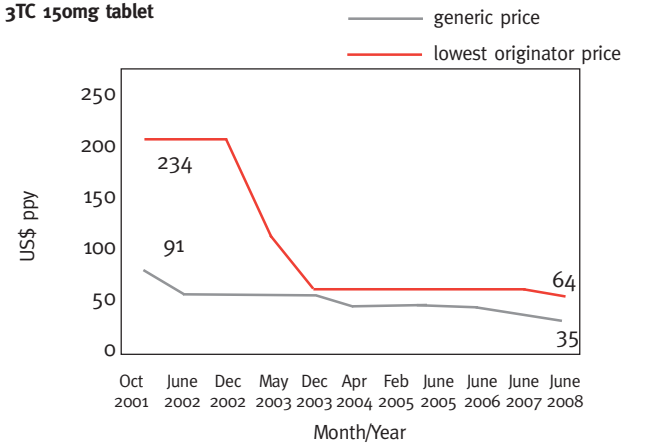
General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults and adolescents, and for first-line only for children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Epivir.
- First approval by U.S. Food and Drug Administration (FDA): November 1995.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2007: US$309 million; 2006: US$398 million; 2005: US$398 million; 2004: US$549 million.[60,61]
- The basic patent on 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.[71,72]
- GSK obtained a licence from IAF to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which are due to expire around 2012.[78]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
Eligibility restrictions		See Annex 2	None	None	None	None	None	None
3TC 150mg tablet	2	**64 (0.087)**	**40 (0.055)**	**35 (0.048)**	**37 (0.050)**	**42 (0.058)**	**43 (0.059)**	**52 (0.071)**
3TC 300mg tablet	1		**24 (0.067)**	50 (0.137)				
3TC 10mg/ml oral solution	10ml	**84 (0.023/ml)**	**33 (0.009/ml)**	**37 (0.010/ml)**				
3TC 25mg granules	--							(2.200)
3TC 50mg granules	--							(2.700)

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.
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were six WHO prequalified generic sources of 3TC 150mg and the lowest price product is shown here.

Price reductions for the originator product have been 73% since 2001 while generic prices have dropped by 62%.

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. 3TC is also active against Hepatitis B, and hence plays an important role in co-infected patients.

Patents: As seen above, the price of 3TC decreased dramatically after the onset of generic competition. Generic competition originated in countries with manufacturing capacity where 3TC 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$1,672 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 widely used in children. Generic manufacturers have been developing both double and triple fixed-dose combinations containing 3TC. Today, however, there is only two WHO prequalified triple FDC containing 3TC for paediatrics. To give a clinician flexibility in the prescribing of ARV regimens, there is a need for a single simple adapted formulation of 3TC. The Paediatric Antiretroviral Working Group at WHO has given "important" priority to the development of a 30mg tablet. 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.[17]

STAVUDINE (d4T)

General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.[79]
- Originator company, and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- First approval by U.S. Food and Drug Administration (FDA): December 1994.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2006: US$155 million; 2005: US$216 million; 2004: US$272 million; 2003: US$354 million.[35,36]
- d4T was the result of U.S. public sector research. It was originally synthesized by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.[80] 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.[81] This patent should have expired around December 2007, but the protection was extended until the end of 2008 in the U.S. and 2011 in most European countries. BMS markets d4T under a marketing and distribution licence from Yale University.

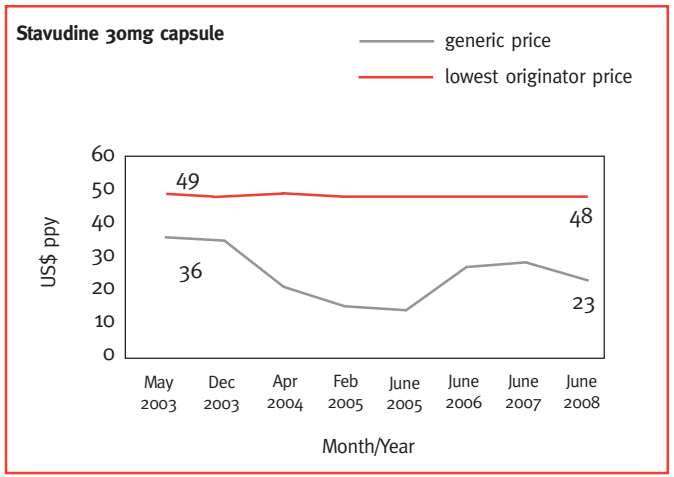
Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Bristol-Myers Squibb		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
		Category 1	Category 2						
Eligibility restrictions		See Annex 2		None	None	None	None	None	None
d4T 15mg capsule	--	**(0.082)**	**(0.093)**	**(0.029)**	(0.025)	(0.022)			
d4T 20mg capsule	--	**(0.089)**	**(0.092)**	**(0.030)**	(0.023)	(0.025)			
d4T 30mg capsule	2	**48 (0.066)**	**67 (0.092)**	**23 (0.032)**	19 (0.026)	22 (0.030)	**24 (0.033)**	**28 (0.039)**	**27 (0.037)**
d4T 40mg capsule	2	**55 (0.075)**	**67 (0.092)**	**28 (0.038)**		26 (0.036)	**31 (0.042)**	**34 (0.047)**	**30 (0.042)**
d4T 1mg/ml powder for syrup	20ml	**51 (0.007/ml)**	**58 (0.008/ml)**	**66 (0.009/ml)**	44 (0.006/ml)				
d4T 5mg granules	--								(2.000)
d4T 10mg granules	--								(2.500)

(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.

Note: BMS second category pricing is provided in South African Rand. These were converted to US$ on the date the prices were received, and hence fluctuations in the US$ do impact these prices.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest price quoted for eligible developing countries since 2003.

As of June 2008, there were four WHO prequalified generic sources of d4T. The lowest available generic price is therefore shown here.

Spotlight on access issues:

Stavudine (d4T) is a widely-used ARV in first-line regimens. It has been an important component of the fixed-dose combinations that have fostered treatment scale-up in resource-limited settings. However, the 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to less toxic first-line regimens. We can therefore expect to see a decrease in the use of this product in the future.

BMS's differential pricing structure limits access to these prices to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries paying more than US$1,950 per patient year, which is prohibitive for many of these countries.[66]

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.

However, in South Africa, where BMS marketed d4T under an exclusive licence from Yale, it was 34 times more expensive than generic versions available in other countries. In March 2001, a patent controversy happened over this elevated price of d4T in South Africa, coupled with the fact that the medicine has been developed with public funds. After pressure from researchers, students, and access advocates, Yale renegotiated its licence with BMS to allow the importation of more affordable generic versions of d4T in South Africa.[80]

Paediatrics: d4T 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, however, only two d4t-containing triple FDCs are WHO prequalified.

TENOFOVIR DISOPROXIL FUMARATE (TDF)

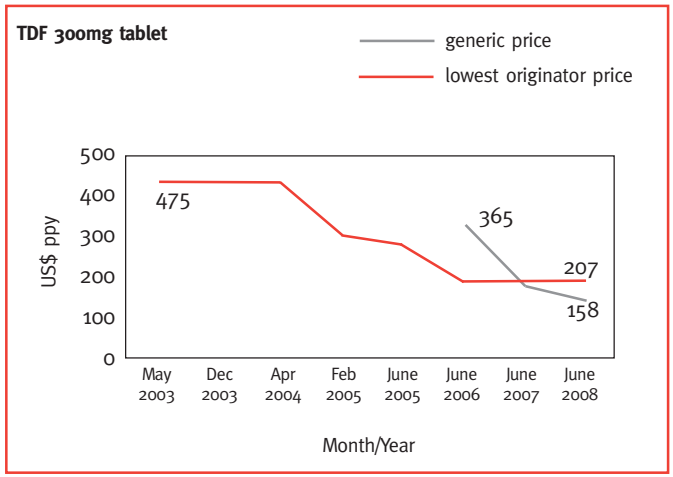
General information

- Therapeutic class: nucleotide reverse transcriptase inhibitor (NtRTI).
- Indicated for first- and second-line, for adults and adolescents (WHO 2006 guidelines).[15]
- Originator company, and product brand name: Gilead, Viread.
- First approval by U.S. Food and Drug Administration (FDA): October 2001.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2007: US$613 million; 2006: US$689 million; 2005: US$778 million; 2004: US$783 million.[69,70,82,83]
- 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.[84]
- Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997[85] and to the fumarate salt of tenofovir disoproxil in 1998.[86] These are due to expire in 2017 and 2018, respectively.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Gilead		Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy
		Category 1	Category 2				
Eligibility restrictions		See Annex 2		None	None	None	None
TDF 300mg tablet	1	**207 (0.567)**	**365 (1.000)**	151 (0.415)	128 (0.350)	**158 (0.433)**	194 (0.532)

(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.
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest price quoted for eligible developing countries since 2003.

As of June 2008, there was one WHO prequalified generic source of TDF, which is shown here.

There has been a 57% decrease in the generic price since 2006, and a 56% decrease in the lowest originator price since 2003.

TENOFOVIR DISOPROXIL FUMARATE (TDF)

Spotlight on access issues:

The 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to either AZT or TDF-based regimens.[15]

Additionally, in 2007, WHO convened a technical consultation to simplify the choice of second-line regimens, and has recommended tenofovir disoproxil fumarate (TDF) in combination with 3TC as one of the two recommended NRTI backbones (the second option being ABC/ddI) to be added to a boosted PI for patients whose initial regimen was 3TC/d4T/NVP. [57]

TDF is also active against Hepatitis B and therefore plays an important role in co-infected patients.

As a result of these changes, the use of TDF is expected to increase, which will have a substantial impact on the budgets of HIV/AIDS treatment programmes. The previously recommended d4T-based first-line regimens now cost less than US$100 per patient per year. Changing to a TDF-based first-line in a fixed-dose combination would increase the cost between four and elevenfold (see graphs 2 and 3).

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

Patents: Gilead has applied for patent 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, and are still under review.

Following oppositions to its patent applications in India, Gilead signed licensing agreements with ten Indian generic manufacturers in September 2006 for the production of generic TDF and combinations containing TDF, in exchange for a 5% royalty. Gilead has stipulated in these licences a pre-defined list of countries to which companies can export. Additionally Gilead's licences limit the supply of Active Pharmaceutical Ingredient (API) by its licencees to pre-approved producers only.[87] Not all countries and patients can therefore benefit from this competition.

However, it is disappointing that almost two years after the signing of these agreements, only four companies, three of which are under a licence from Gilead, reported manufacturing generic TDF for this publication.

Additionally, 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$1,380 per patient per year, over ten times the best generic price offered.

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: TDF is not currently approved for children younger than 18 years in the U.S. Gilead is currently sponsoring two Phase III trials, the first involving adolescents (12-18yrs) and the second looking at an oral powder formulation for children (2-12 years). Results from these studies will contribute to the urgent need for dosing information and information on medium- and long-term toxicity in children.

ZIDOVUDINE (AZT, ZDV)

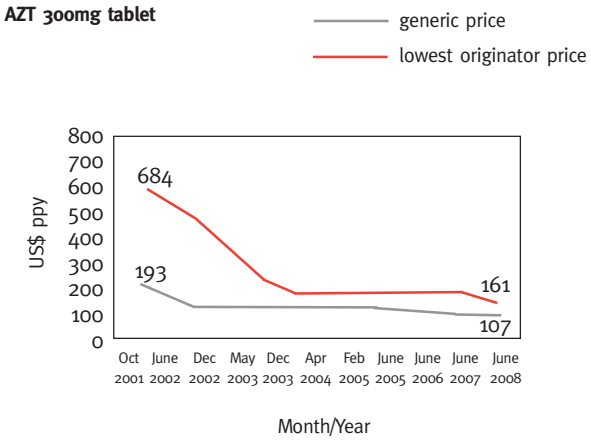
General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Retrovir.
- First approval by U.S. Food and Drug Administration (FDA): March 1987.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: In 2005: US$84 million; 2004: US$80 million. After 2005, there are no sales figures for this product listed in the company's annual report.[58,59]
- 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. Nevertheless, 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 now.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
Eligibility restrictions		See Annex 2	None	None	None	None	None	None
AZT 300mg tablet	2	**161 (0.221)**	**110 (0.150)**	**107 (0.146)**	99 (0.135)	104 (0.142)	**115 (0.157)**	
AZT 100mg capsule	--	**(0.122)**	**(0.100)**	**(0.050)**				
AZT 250mg capsule	--	**(0.276)**						
AZT 10mg/ml syrup	20ml	**234 (0.032/ml)**	**73 (0.010/ml)**	**73 (0.010/ml)**				
AZT 25mg granules	--							(2.850)
AZT 50mg granules	--							(3.350)

(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. Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were three WHO prequalified generic sources of AZT 300mg. The lowest available generic price is therefore given here. Since 2001, the originator price has decreased 76%, while the generic price has decreased 46%.

Spotlight on access issues:

The price of zidovudine (AZT) decreased dramatically after generic competition started in 2001. Such competition was possible because GSK could not obtain patents in countries with generic production capacity. AZT will continue to be an important ARV in the scale-up of ARV treatment in the developing world.

The 2006 WHO treatment guidelines suggest countries start to consider moving away for d4T-based regimens to either AZT- or TDF-based regimens.[15]

Additionally, in 2007, WHO convened a technical consultation to simplify the choice of second-line regimens, and AZT in combination with 3TC was the recommended NRTI backbone to be added to a boosted PI for patients whose initial regimen was TDF/3TC/EFV.[57]

Paediatrics: AZT is approved for use and widely used in children. Generic manufacturers have been developing both double and triple fixed-dose combinations including AZT. Today, however, there are no WHO prequalified paediatrics FDCs containing AZT. To give a clinician flexibility in the prescribing of ARV regimens, there is a need for a single simple adapted formulation of AZT. The Paediatric Antiretroviral Working Group of WHO has given "important" priority to the development of a 60mg tablet.[17]

General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, for adults and adolescents (WHO 2006 guidelines).[15]
- Originator company, and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approval by U.S. Food and Drug Administration (FDA): 20 June 2003.[19]
- Not included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product for 2007: US$1124 million; 2006: US$931 million; 2005: US$696 million; 2004: US$369 million; 2003: US$81 million.[35,88,89]
- The basic patent was filed in April 1997 by Novartis and is expected to expire in April 2017.[90]
- Bristol-Myers Squibb (BMS) is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998[91] and on a process for preparing the bisulfate salt and novel forms in 2005.[92]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	BMS	
		Category 1	Category 2
Eligibility restrictions		See Annex 2	
ATV 150mg capsule	2*	353 (0.484)	425 (0.582)
ATV 200mg capsule	--	(0.602)	(0.732)

* The dose of ATV must be boosted with RTV 100mg once a day.[15]

Note: BMS second category pricing is provided in South African Rand. These were converted to US$ on the date the prices were received, and hence fluctuations in the US$ do impact these prices.

Spotlight on access issues:

Atazanavir (ATV) is one of the five boosted protease inhibitors recommended by WHO in the 2006 guidelines for second-line treatment. No guidance was given in the guidelines however on how to prioritize the choice. In 2007, WHO convened a technical consultation to simplify the selection of boosted PIs for use in second-line regimens, and ATV (in combination with ritonavir (RTV)) was one of the two PIs recommended.[57]

Of the two, ATV is the most patient-friendly PI, as it requires the patient to take only two 150mg pills once a day. ATV, like all PIs (with the exception of nelfinavir (NFV)), require boosting with RTV. Abbott's monopoly on RTV and the temperature-sensitive nature of the currently-available formulation of RTV may limit the use of this product in the developing world. There is an urgent need for generic manufacturers to supply a heat-stable ATV/r fixed-dose combination.

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. Some of these patents have already been granted in Brazil and China. In India, where the applications are still under examination, civil society organisations filed a pre-grant opposition regarding Novartis' basic patent on the ground of lack of novelty,[43] but the other patent applications warrant additional patent pre-grant oppositions. A decision on the patent application is pending.

In February 2006, BMS granted technology transfer and voluntary licence to two generic manufacturers (Emcure and Aspen) to manufacture and sell ATV. Under the conditions of the licence, sales of these products are royalty-free but are restricted to sub-Saharan Africa. BMS has a separate agreement with Emcure that covers India.[93] Licensing agreements in India should not be necessary if patent oppositions are successful. If the patent is granted, the licensing agreements should be offered to many more manufacturers and allow export beyond sub-Saharan Africa, ensuring the widest possible access to ATV at affordable prices. The only alternative will be for countries to use compulsory licences to enable unrestricted competition from generic manufacturers.

In February 2008, Emcure received U.S. FDA tentative approval for the 100mg, 150mg and 200mg ATV capsules. Emcure was invited to provide information for this publication, but did not have prices available to contribute.

BMS's differential pricing structure is limited to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries paying more than US$6,000 ppy, which is prohibitive for many of these countries.[66] The required addition of RTV as a booster must also be considered in the final cost of using ATV.

Paediatrics: In March 2008, ATV was approved for use in children between six and 18 years of age. WHO has recently recommended early treatment for all HIV-positive children, and children who have been exposed to NVP either through their mother or through a single dose in a PMTCT programme. WHO recommends these children should be started on a PI-based regimen.[94] Today, the only option for these children is the LPV/r formulations. To simplify treatment for the youngest patients, there is an urgent need for studies on ATV to be completed in children and infants, and child-adapted formulations to be made available.

DARUNAVIR (DRV)

General information

- Therapeutic class: protease inhibitor (PI).
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced patients, such as those with HIV-1 strains resistant to more than one protease inhibitor for adults[95].
- Originator company and product name: Tibotec (a division of Ortho Biotech Products), Prezista.
- First approved by the U.S. Food and Drug Administration (FDA) on 23 June 2006.[19]
- Not included in the WHO Model List of Essential Medicines (EML).[20]
- Darunavir basic patent applied for by Searle and Monsanto in August 1993,[96] and due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to darunavir in 1999[97] and licenced them to Tibotec for development.[98] Tibotec later applied for patents related to improved forms and combinations of darunavir.[99,100]

Price information:

Prices in US$ quoted by companies for eligible developing countries

Tibotec have indicated that the price offered will not exceed US$3 per day for sub-Saharan African countries on an FOB basis. This relates to an approximate yearly cost of US$1,095.

Spotlight on access issues:

Tibotec Pharmaceuticals signed a royalty-free, non-exclusive licence agreement with Aspen Pharmacare of South Africa on 4 April 2007. This grants Aspen the right to register, package and distribute darunavir (DRV) in sub-Saharan Africa.[101] This agreement excludes other low- and middle-income countries, for which the developed world price of over US$10,000 per patient year is likely to be prohibitive.[66]

DRV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's monopoly on RTV and the temperature-sensitive nature of the currently-available formulation of RTV may limit the use of this product in the developing world.

Patents: Even though basic patents related to darunavir could not be applied for in India before 1995, Tibotec has applied for several patents in India related to new forms and combinations of darunavir, some of which have been opposed by generic manufacturers. Most of these patent applications remain under review at the Indian patent office.

Paediatrics: The safety and efficacy of DRV in children has not been established.

FOSAMPRENAVIR (FPV or f-APV)

General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, for adults (WHO 2006 guidelines).[15]
- Originator company and product brand name: GlaxoSmithKline and VertexPharmaceuticals, Lexiva.
- First approved by the U.S. Food and Drug Administration (FDA) on 20 October 2003.[19]
- Not included in the WHO Model List of Essential Medicines (EML).[20]
- Basic patent applied for by Vertex Pharmaceuticals in March 1998,[102] and due to expire in 2018. Fosamprenavir, a phosphate ester prodrug of amprenavir,[103] was developed and launched by GSK, under licence from Vertex.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK
Eligibility restrictions		see Annex 2
Fosamprenavir 700mg tablet	2*	1222 (1.674)
Fosamprenavir 50mg/ml suspension	12ml	648 (0.148/ml)

*The dose of FPV must be boosted with RTV 100mg twice a day.[15]

Spotlight on access issues:

Fosamprenavir (FPV) is one of the five boosted protease inhibitors recommended by WHO in the 2006 guidelines for second-line treatment. No guidance was given in the guidelines however on how to prioritize the choice. In 2007, WHO convened a technical consultation to simplify the selection of boosted PIs for use in second-line regimens and FPV was not identified as one of the priority products. 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.[57]

FPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's monopoly on RTV and the temperature-sensitive nature of the currently-available formulation of RTV may limit the use of this product in the developing world.

Patents: Patent applications have been filed for in many developing countries. There are no generic formulations of this product available today.

Paediatrics: FPV is approved for use in children and a paediatric formulation is available.

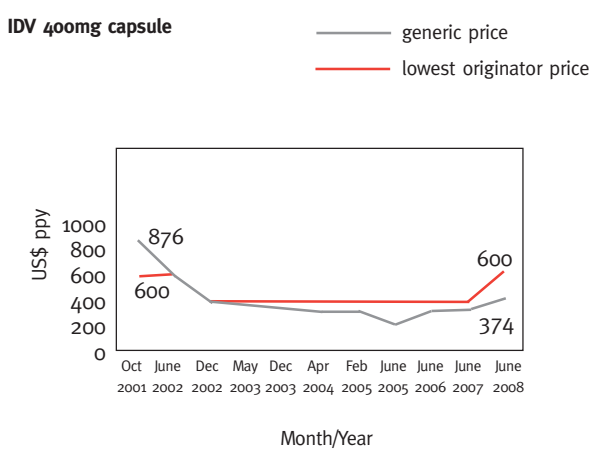
General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, for adults (WHO 2006 guidelines).[15]
- Originator company and product brand name: Merck, Crixivan.
- First approval by U.S. Food and Drug Administration (FDA): March 1996.[19]
- Not included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- There are no sales figures for this product listed in the company annual report.
- Basic patent filed for by Merck in 1992 and is due to expire in 2012 in countries granting 20-year patents.[103]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Merck		Aurobindo	Cipla	Hetero	Ranbaxy
		Category 1	Category 2				
Eligibility restrictions		See Annex 10		None	None	None	None
400mg capsule	4*	**394 (0.270)**	**686 (0.470)**	365 (0.250)	422 (0.289)	**374 (0.256)**	381 (0.261)

*The dose of IDV must be boosted with RTV 100mg twice a day.[15]
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there was one WHO prequalified generic source of IDV 400mg, which is shown here.

Spotlight on access issues:

Indinavir (IDV) is one of the five boosted protease inhibitors recommended by WHO in the 2006 guidelines for second-line treatment. No guidance was given in the guidelines however on how to prioritize the choice. In 2007, WHO convened a technical consultation to simplify the selection of boosted PIs for use in second-line regimens and IDV was not identified as one of the priority products. The main concern was that at a standard dose of 800mg IDV with 100mg RTV twice a day, it was less well tolerated than other PIs, particularly in hot climates.[57]

There have been some small studies to support a lower dose of 400/100mg IDV/RTV twice a day with the aim of reducing 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)), require boosting with (RTV). Abbott's monopoly on RTV and the temperature-sensitive nature of the currently-available formulation of RTV may limit the use of this product in the developing world.

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

Paediatrics: The optimal dosing regimen for the use of IDV in paediatric patients has not been established and no paediatric formulation exists.[104]

LOPINAVIR/RITONAVIR (LPV/r)

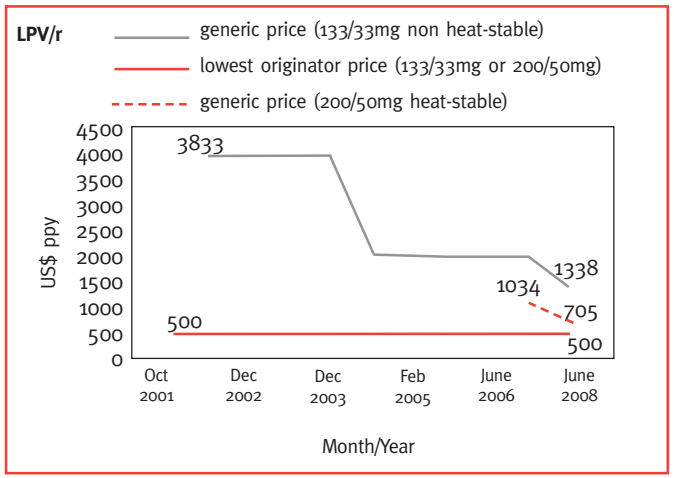
General information

- Therapeutic class: boosted Protease Inhibitor (PI) in double fixed-dose combination
- Indicated for second-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- First approval by U.S. Food and Drug Administration (FDA): soft-gel capsules were approved in September 2000. Heat-stable tablets were approved in October 2005.[19]
- Originator company, and product brand name: Abbott Laboratories, Kaletra, Aluvia.
- Included in the WHO Model List of Essential Medicines (EML) (only soft gel capsules).[20]
- World sales of originator product: 2007: US$1.32 billion (16.7% increase over 2006 figures); 2004: US$897 million; 2003: US$754 million; 2002: US$551 million; 2001: US$292 million.[105,106]
- Most patents related to RTV also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.[107] In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997[108] which are due to expire in 2017. Patents were also filed in 2004 to protect the heat-stable tablet formulation[109] which, if granted, would run until 2024.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Abbott		Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)
		Category 1	Category 2				
Eligibility restrictions		See Annex 2		None	None	None	None
LPV/r 133/33mg soft gel capsule	6	**500 (0.228)**	**1000 (0.457)**		1338 (0.611)	447 (0.204)	
LPV/r 200/50mg tablet (heat-stable)	4	**500 (0.342)**	**1000 (0.685)**	768 (0.526)	1339 (0.917)		705 (0.483)
LPV/r 80 + 20mg/ml oral solution	4ml	**200 (0.137/ml)**	**400 (0.274/ml)**				
LPV/r 100/25mg tablet (heat-stable)	2	125 (0.171)	250 (0.343)	293 (0.401)			204 (0.279)

(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.
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest quoted price for eligible developing countries since 2002.

As of June 2008, there was no WHO prequalified generic source of lopinavir/ritonavir. The lowest available generic price for both the heat-stable tablet and soft-gel capsule are considered for the graph. As both formulations from the originator are priced the same, they are shown on the graph as one.

Spotlight on access issues:

Lopinavir/ritonavir (LPV/r) is one of the five boosted protease inhibitors recommended by WHO in the 2006 guidelines for second-line treatment. No guidance was given in the guidelines however on how to prioritize the choice. In 2007, WHO convened a technical consultation to simplify the selection of boosted PIs for use in second-line regimens and LPV/r was one of the two PIs recommended.[57]

The heat-stable formulation of LPV/r manufactured by Abbott is now marketed in developing countries. In comparison to the older soft-get 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. Generic manufacturers are now entering the market and this is having a positive effect on the market, as prices start to decline. The Clinton Foundation's most recent announcement has some generic manufacturers offering prices of US$550 ppy (a 20% reduction from the CF 2007 price announcement).

Patents: In India, Abbott has applied for several patents related to LPV/r, or to the individual components, a number of which have been opposed by civil society organisations[110] 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 would be expected to drive prices down as demand increases, will be under threat.

In Thailand, where Abbott holds patents, the price of LPV/r was US$2,200 ppy in 2007. In January 2007, the Ministry of Health of Thailand issued a compulsory licence to import more affordable generic versions of the drug from India.[38] 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. However, a positive result was that Abbott reduced its price offer for middle-income countries to US$1,000 ppy. For Thailand to be able to benefit from this price, however, Abbott stipulated that the country would have to retract its compulsory licence, which it did not do. Thailand is today importing generic LPV/r from India at US$898 ppy.[111]

Paediatrics: LPV/r is approved for use in children. In early 2007, Abbott released a heat-stable paediatric 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 this it must be stored at below 25°c for only six weeks. The solution is also 42% alcohol and has a very unpleasant taste.

Recent changes in WHO guidelines recommending that all HIV-positive children under one year old start ARV therapy as soon as possible regardless of clinical state, combined with the recommendation to start all children exposed to NVP on a PI-based regimen, should result in an increased demand for this combination for very young children. There is an urgent need for a more adapted formulation for young children.

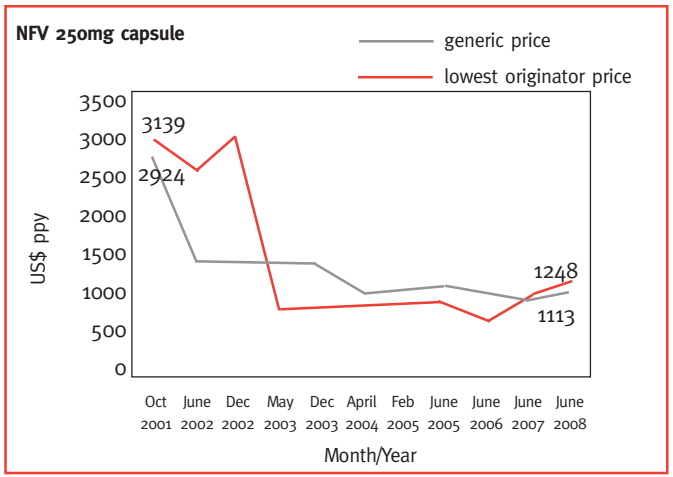
General information

- Therapeutic class: protease inhibitor (PI).
- Indicated only for second-line in adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: Roche, Viracept.
- First approval by U.S. Food and Drug Administration (FDA): 14 March 1997.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2004: US$259 million. After 2004, there are no sales figures listed in the company's annual report.[112]
- Basic patent applied for in 1994 by Agouron Pharmaceuticals,[113] and 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. NFV is supplied by Roche outside the US, Canada and Japan.[114]

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Roche		Cipla	Hetero
		Category 1	Category 2		
Eligibility restrictions		See Annex 2		None	None
NFV 250mg tablet	10	**1248 (0.342)**	**2562 (0.702)**	1113 (0.305)	1132 (0.310)
NFV 50mg/g oral powder	24g	**2243 (0.256/g)**	**2593 (0.296/g)**		

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were no WHO prequalified generic sources of NFV. The lowest available generic price is therefore shown here.

Roche quotes prices in Swiss Francs (CHF), which are converted to US$ on the date received and hence fluctuations in the US$ do have an impact on prices used in the graph.

NELFINAVIR (NFV)

Spotlight on access issues:

Nelfinavir (NFV) is the only PI that does not require boosting with ritonavir (RTV). The large pill burden (ten tablets a day for an adult) and the high price make it a less-desirable option when selecting a PI. However, the fact that it does not need to be given with RTV means that the heat-sensitive nature of the current RTV formulation does not need to be a consideration. This had made the drug an attractive option for some developing countries in the past.

In June 2007, Roche recalled all batches of NFV due to high levels of Ethyl Methane Sulphonate (EMS), a byproduct 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.[115,116,117]

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.

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, together with the small demand for the second-line drug, contributes to the high price of the drug. 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.

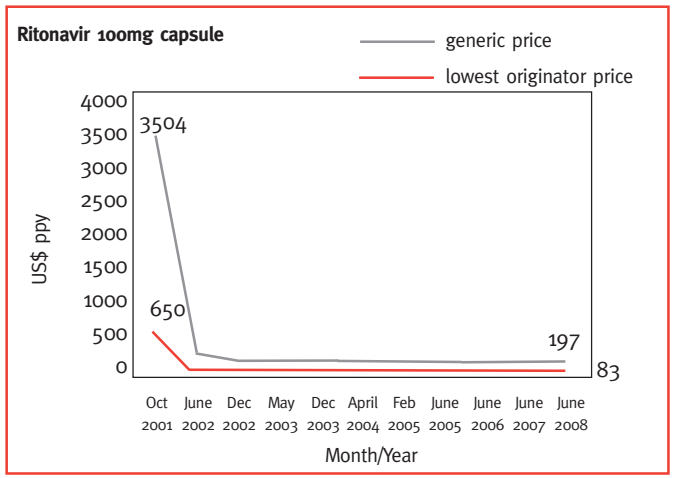
General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line as a booster, for adults, adolescents and children (WHO 2006 guidelines). [15,16]
- 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 29 June 1999 for capsules.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- World sales of originator product: 2004: US$194 million; 2003: US$93 million; and 2002: US$122 million.[105]
- Basic patent applied for by Abbott in 1993[118] and due to expire in 2013. Subsequently, Abbott applied for many additional patents related to pharmaceutical compositions of RTV in 1998[108] or for new forms of RTV, such as the crystalline polymorph in 1999.[119] These are due to expire in 2018-2019.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose used as booster	Abbott	Cipla	Hetero	Strides
Eligibility restrictions		See Annex 2	None	None	None
100mg capsule	2	**83 (0.114)**	313 (0.429)	197 (0.270)	365 (0.500)
80mg/ml oral solution	--	**(0.093/ml)**			

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there was no WHO prequalified generic source of RTV. 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 PIs (with the exception of Nelfinavir (NFV)), must be boosted with this drug. RTV today is only available from Abbott as a soft-gel capsule that requires refrigeration. The heat-sensitive nature of the formulation makes it extremely ill-adapted for use in the developing countries.

Abbott has developed a heat-stable fixed-dose combination of LPV and RTV (LPV/r) that was approved in the U.S. in 2005, but today the heat-stable RTV alone is not yet available. Abbott has provided no clear reasons for the delay in bringing this product to market, despite requests to Abbott from the EMEA.[142] The development and marketing of a heat-stable RTV formulation would be critical to eliminating the heat-stable boosted PI monopoly that currently exists with LPV/r.

Generic manufacturers are working on the development of heat-stable RTV tablets, however, the progress has been slow. For a generic product to enter the market, it must show that the same blood levels of the drug are obtained in humans as with the originator product (this is known as bioequivalence). This is more difficult to show if the formulations are different, for example a capsule versus a tablet, as they may be absorbed into the bloodstream from the gastrointestinal tract at different rates. Today, the originator RTV product is a non heat-stable capsule, yet the technology involved in creating heat-stable RTV requires formulation to be in tablet form. The lack of an originator reference for the heat-stable tablet therefore makes the development of generic heat-stable versions more difficult.

Patents: Although the basic patent disclosing RTV could not be applied for in India, Abbott has applied for various patents on improved formulations of RTV, which renders the extent of future generic competition unclear. A pre-grant opposition to an application related to a polymorph of RTV was filed by civil society organisations in India in September 2006.[110] 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.

Paediatrics: Ritonavir 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 has given "important" priority to the development of a 25mg heat-stable RTV tablet.[17]

SAQUINAVIR (SQV)

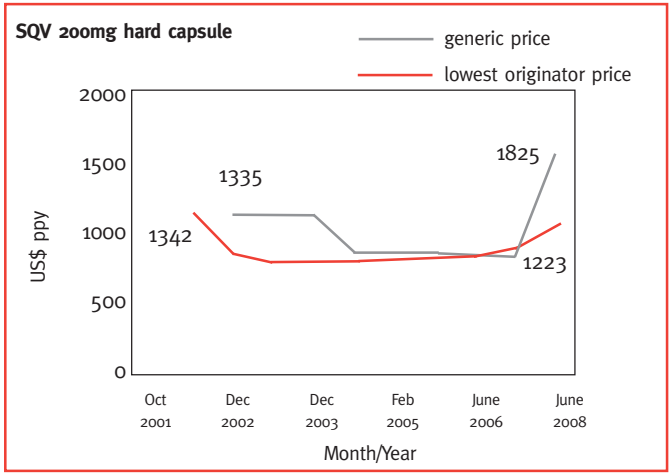
General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, to be used boosted by ritonavir, for adults, adolescents and children (WHO 2006 guidelines).[15]
- Originator company, and product brand name: Roche, Invirase.
- First approval by U.S. Food and Drug Administration (FDA): December 1995.[19]
- Included in the 15th Edition WHO Model List of Essential Medicines (EML).[20]
- The basic patent was applied for by Roche in 1990[120] and is due to expire in 2010.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Roche		Cipla	Hetero
		Category 1	Category 2		
Eligibility restrictions		See Annex 2		None	None
SQV 200mg hard capsule	10*	**1223 (0.335)**	**2562 (0.702)**	1825 (0.500)	
SQV 500mg tablet	4*	**1127 (0.772)**	**2559 (1.753)**		1533 (1.050)

* The dose of SQV must be boosted with RTV 100mg twice a day.[15]
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there was no WHO prequalified generic source of SQV. The lowest available generic price is therefore shown here.

Spotlight on access issues:

Saquinavir (SQV) is one of the five boosted protease inhibitors recommended by WHO in the 2006 guidelines for second-line treatment. No guidance was given in the guidelines however on how to prioritize the choice. In 2007, WHO convened a technical consultation to simplify the selection of boosted PIs for use in second-line regimens and SQV was not identified as one of the priority products. Boosted SQV appears to be slightly less potent than the other boosted PIs and in the original formulation has a high pill count (ten capsules).[57]

In 2004, Roche marketed in the U.S. a 500mg tablet of SQV that reduced the pill count from ten to four tablets. 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 severely limited, as its use is fairly limited.

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.[121]
- Originator company and product brand name: Boehringer Ingelheim Pharmaceuticals, Aptivus.
- First approved by the U.S. Food and Drug Administration (FDA) on 23 June 2005.[19]
- Not included in the WHO Model List of Essential Medicines (EML).[20]
- Basic patent applied for by Upjohn in May 1995,[122] and due to expire in 2015. In 1998, Pharmacia & Upjohn applied for additional patents related to pharmaceutical formulations suitable for the oral administration of TPV.[123,124] In January 2000, BI acquired worldwide rights for TPV.

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Boehringer Ingelheim was invited to contribute a price for this publication and has communicated that tipranavir (TPV) is available through its compassionate use programme and that they are currently filing for registration in various countries.

TPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with RTV. This need for boosting with RTV and the temperature sensitivity of current formulations of RTV may limit the use of this product in the developing world.

Patents: TPV patents have been filed widely in developing countries with generic production capacity, such as Brazil. In Brazil, where the patent applications are under review, the drug regulatory agency (ANVISA), has advised for the rejection of the basic patent application. In Brazil, ANVISA has to give “prior consent” for any patent application related to a medicine.[125] In early 2007, civil society raised concerns over the registration procedure of TPV in Brazil, although the medicine has been tested in Brazilian patients in 14 research centres since February 2004. The registration was only filed with ANVISA at the end of February 2008, after civil society groups questioned the lack of registration, almost three years after U.S. FDA and EMEA approvals. Brazilian civil society groups' strong reaction was also based on the suspicion that the company did not want to register the product in the country unless they had the guarantee that the patent would be granted by the Brazilian patent office.[126,127]

Paediatrics: TPV is not currently approved for use in children.

ABACAVIR/LAMIVUDINE (ABC/3TC)

General information

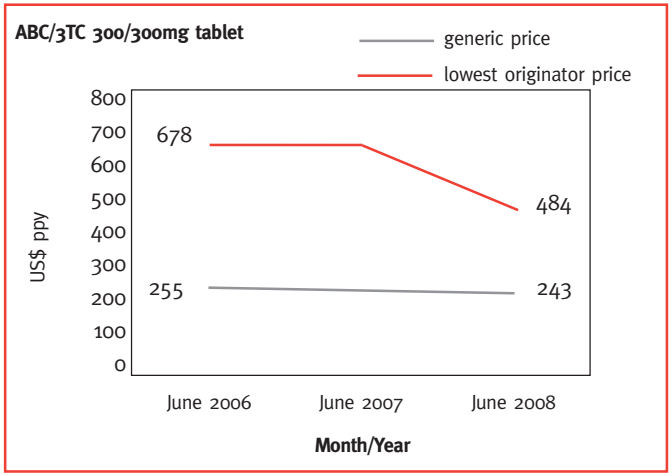
- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Kivexa (EU), Epzicom (U.S).
- First approval by U.S. Food and Drug Administration (FDA): August 2004.[19]
- 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.[20]
- World sales of originator product: 2007: US$641 million; 2006: US$475 million; 2005: US$233 million.[59,60,61]
- Most patents on ABC or 3TC also affect this combination. In addition, GSK applied for patents more specifically related to the combination.[128]

For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Cipla	Matrix (CF)
Eligibility restrictions		See Annex 2	None	None
ABC/3TC 600/300mg tablet	1	484 (1.326)	243 (0.667)	
ABC/3TC 60/30mg tablet	4			219 (0.150)

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



Evolution of the lowest price quoted for eligible developing countries since 2006.

As of June 2008, there were no WHO prequalified generic sources of ABC/3TC. The lowest available generic price is therefore shown here.

There has been a decrease of 29% in the originator price since the introduction of the generic product.

Spotlight on access issues:

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

Paediatrics: For children who need this combination, the current available options are the use of two different syrups. The use of fixed-dose combinations has been shown to increase the adherence and increase accuracy in dosing. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric formulation of ABC/3TC FDC a “high” priority.[17]

General information

- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40 mg to d4T 30 mg for all weight categories of patients.[79]
- 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.[20]
- Individual patents on 3TC or 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.

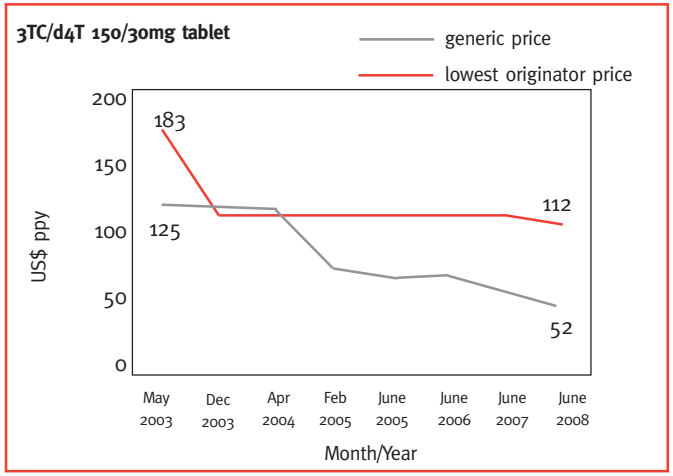
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
Eligibility restrictions		None	None	None	None	None	None
3TC/d4T 150/30mg tablet	2	53 (0.072)	**52 (0.071)**	46 (0.063)	55 (0.075)	**61 (0.083)**	52 (0.071)
3TC/d4T 150/40mg tablet	2	55 (0.075)		52 (0.071)	61 (0.083)	**64 (0.088)**	**55 (0.075)**
3TC/d4T 30/6mg dispersible tablet	4		51 (0.035)				
3TC/d4T 60/12mg dispersible tablet	2		50 (0.068)				
3TC/d4T 20/5mg dispersible tablet	--					(0.038)	
3TC/d4T 40/10mg dispersible tablet	--					(0.053)	

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest price quoted for eligible developing countries since 2003.

As of June 2008, there were two WHO prequalified generic sources of 3TC/d4T 150/30mg. The lowest available generic price is therefore shown here. As there is no originator FDC, the price shown for the originator is for the combination of the two single originator products.

There has been a 39% decrease in the originator price and a 58% decrease in generic price since 2003.

Spotlight on access issues:

This combination has been an important formulation that has fostered treatment scale-up in resource-limited settings. However, the 2006 WHO guidelines for adults suggest countries start to consider moving away from d4T-based regimens to less-toxic firstline regimens.[15] We can therefore expect to see a decrease in the use of this product in the future.

Patents: Generic companies in certain developing countries were able to develop these FDCs because patents on the individual products did not exist. The FDC is not available in developed countries or in countries such as China, 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 the NVP at a lower dose for the first two weeks to minimize the side effects. Today, the option is for the child to take two different syrups, one of which (the d4T paediatric formulation), is ill-adapted as it is supplied as a powder requiring reconstitution and subsequent refrigeration.

For simplification, there is an urgent need for a quality-assured double FDC to allow children to be safely and accurately dosed while starting treatment. Today, there are no WHO prequalified 3TC/d4T FDC tablets available. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric formulation of 3TC/d4T FDC an "urgent" priority.[17]

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 adults, adolescents and children (WHO 2006 guidelines).[15,16]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.[79]
- Included in the WHO Model List of Essential Medicines (only the d4T 30mg presentation) (EML).[20]
- 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.[20]
- Individual patents on 3TC, d4T or 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 FDC. Cipla first developed the fixed-dose combination and applied for patents in several African countries.

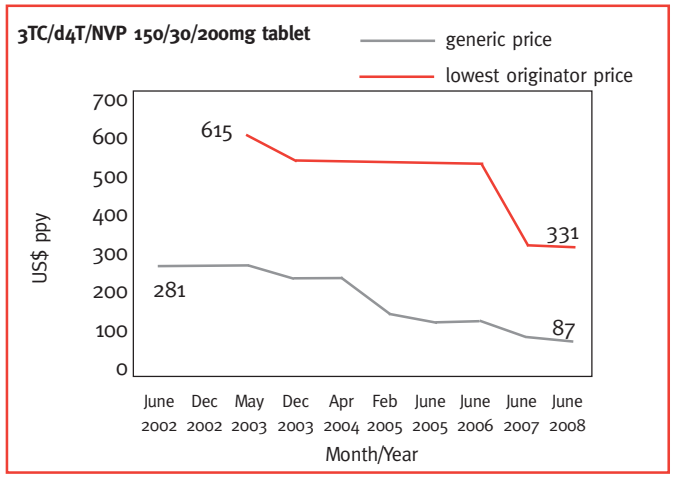
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
Eligibility restrictions		None	None	None	None	None	None
3TC/d4T/NVP 30/6/50mg dispersible tablet	4		**117 (0.080)**	55 (0.038)			
3TC/d4T/NVP 60/12/100mg dispersible tablet	2		**61 (0.084)**	46 (0.063)			
3TC/d4T/NVP 20/5/35mg dispersible tablet	--					(0.054)	
3TC/d4T/NVP 40/10/70mg dispersible tablet	--					(0.092)	
3TC/d4T/NVP 150/30/200mg tablet	2	82 (0.113)	**96 (0.132)**	**87 (0.119)**	104 (0.142)	**99 (0.135)**	102 (0.140)
3TC/d4T/NVP 150/40/200mg tablet	2			**91 (0.125)**	110 (0.175)	**101 (0.139)**	106 (0.145)

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



Evolution of the lowest price quoted for eligible developing countries since 2002.

As of June 2008, there were three WHO prequalified generic sources of 3TC/d4T/NVP. The lowest available generic price is therefore shown here. As there is no originator FDC, the prices used for the originator are for the combination of the three single products.

There has been a decrease of 66% in the generic price since 2002.

Spotlight on access issues:

This combination has played a major role in the scaling up of antiretroviral therapy in the developing world and remains the most-commonly-prescribed therapy in resource-limited settings for first-line treatment in adults. However, the 2006 WHO guidelines for adults suggest countries start to consider moving away from d4T-based regimens to less toxic first-line regimens.[15]

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

Similarly, we have seen a decrease in the number of companies providing prices for the FDC containing 40mg of d4T since WHO recommended the dosage of d4T for all weight categories of adults be 30mg.[79]

Patents: Cipla was able to develop this combination legally 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 ARV treatment to date.

Paediatrics: This is one of the most commonly-used first-line regimens for children today. The Paediatric Antiretroviral Working Group at WHO has now released clear guidance on the ideal strength of each of the individual ARVs in these fixed-dose combinations (FDC), and today there are two formulations prequalified by WHO.[17]

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

General information

- Therapeutic class: two NRTIs + one NNRTI in a co-pack.
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- 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.[20]
- Individual patents on 3TC, d4T or 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.

For information on the individual ARVs contained in this co-pack please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Cipla	Ranbaxy	Strides
Eligibility restrictions		None	None	None
3TC/d4T + EFV 150/30 + 600mg daily co-blister	1 kit (3 tablets)	274 (0.750)	345 (0.945)	
3TC/d4T + EFV 150/40 + 600mg daily co-blister	1 kit (3 tablets)		358 (0.980)	234 (0.641)

Spotlight on access issues:

Generic companies in certain developing countries were able to develop these FDCs because patents on the individual components contained in the combination did not exist. This product is not available in developed countries or in China because of various patents on 3TC, d4T and/or EFV.

NEVIRAPINE + ZIDOVUDINE (NVP + AZT)

General information

- Therapeutic class: one NNRTI + one NRTI co-packaged as single-use sachets.
- Indicated for prevention of mother-to-child transmission.[129]
- Most patents related to NVP or AZT may also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination.

For information on the individual ARVs contained in this co-pack please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily Dose	Strides
Eligibility restrictions		None
NVP 6mg granules + AZT 16mg granules	1 + 14	2.500
NVP 6mg granules + AZT 16mg granules	1 + 56	4.700

Spotlight on access issues:

Paediatrics: The 2006 revised WHO guidelines for Preventing HIV Infection in Infants recommend that children who are born to HIV positive mothers should receive a single dose of nevirapine (sd-NVP) soon after birth, to be followed with either one or four weeks of zidovudine (AZT).[129] The sd-NVP can be problematic to manage in resource-limited settings where many mothers deliver at home. In order for the baby to receive treatment soon after delivery, the mother will need to have been supplied with both the sd-NVP and AZT earlier, with clear instructions on use.

The most common presentation of NVP for infants supplied today is either 100ml or 240ml bottle. Considering the dose of sd-NVP for the newborn child is small (for a 3kg child the dose of NVP suspension would be 0.6ml), the question of how to provide this dose accurately and practically is difficult. The development of the single-use sachets, that have ensured stability at elevated temperatures and can be dissolved in a small amount of water for the child, has helped to overcome this issue.

In 2007, there were an estimated 420,000 new infections in children and 87% of these were in sub-Saharan Africa.[1,143] To help to reduce this alarming number of new children becoming infected through MTCT there is a need for more simple adapted formulations. The Paediatric Antiretroviral Working Group at WHO has classed the development of both AZT and NVP single-use sachets as an "urgent" priority.[17]

General information

- Therapeutic class: one NtRTI + one NRTI in a double fixed-dose combination.
- Indicated for first-line, for adults and adolescents (WHO 2006 guidelines).[15]
- Originator company, and product brand name: Gilead, Truvada.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.[19]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- 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.[20]
- World sales of originator product: 2007: US$1.59 billion; 2006: US$1.19 billion; 2005: US$568 million; 2004: US$68 million[130].
- Most patents related to TDF or to FTC also affect this combination. In addition, Gilead applied for patents specifically related to this combination in 2004,[131] which is due to expire in 2024.

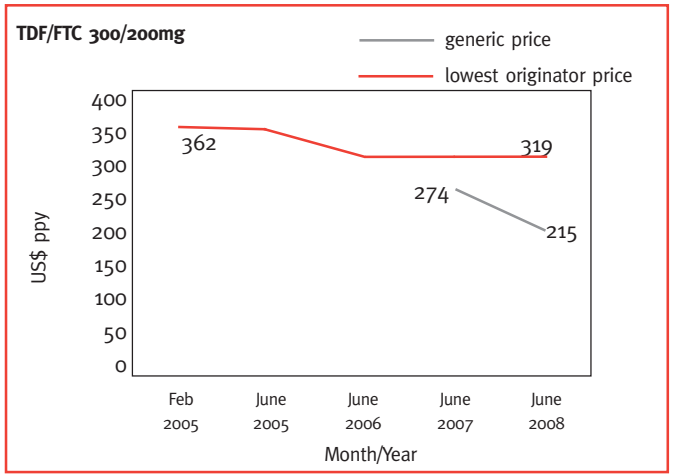
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Gilead		Cipla	Hetero	Matrix (CF)
		Category 1	Category 2			
Eligibility restrictions		See Annex 2		None	None	None
TDF/FTC 300/200mg tablet	1	**319 (0.875)**	**548 (1.500)**	240 (0.658)	215 (0.590)	243 (0.667)

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were no WHO prequalified generic sources of TDF/FTC. The lowest available generic price is therefore shown here.

Spotlight on access issues:

This combination is likely to be widely-used in developing countries as a backbone in first- and second-line regimens. The 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to less toxic AZT- or TDF-based regimens.[15]

Additionally, in 2007, WHO convened a technical consultation to simplify the choice of second-line regimens, and recommended TDF in combination with 3TC or FTC as one of the two recommended NRTI backbones (the second option being ABC/ddI), to be added to a boosted PI for patients whose initial regimen was 3TC/d4T/NVP.[57]

As a result of these changes, the use the TDF/FTC FDC is expected to increase, which will have a substantial impact on the budgets of HIV/AIDS treatment programmes. The previously-recommended d4T-based first-line regimens today cost less than US$100 per patient per year. Changing to a TDF-based first-line in a fixed-dose combination would increase the cost between four and elevenfold (see graphs 2 and 3). Although FTC and 3TC are clinically interchangeable, the price today of the 3TC is almost half that of FTC.

Today, there is no WHO prequalified generic double FDC available.

Patents: This combination could be developed by Indian generic companies because none of the individual components are patented in India today. However, Gilead has applied for patents related to TDF, which are pending a decision from the Indian Patent Office. If these patents are granted in India, generic competition for this product may be affected. Following oppositions to its patent applications in India, Gilead signed licensing agreements with ten Indian generic manufacturers in September 2006 for the production of generic TDF and combinations containing TDF, in exchange for a 5% royalty. Gilead has stipulated in these licences a pre-defined list of countries to which companies can export. Not all countries and patients can therefore benefit from this competition. Additionally Gilead's licences limit the supply of Active Pharmaceutical Ingredients (API) by its licencees to pre-approved producers only.[87]

Paediatrics: TDF is not currently approved for children younger than 18 years.

TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/EFAVIRENZ (TDF/FTC/EFV) FIXED-DOSE COMBINATIONS & CO-PACKS

General information

- Therapeutic class: one NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- Indicated for first-line for adults (WHO 2006 guidelines).[15]
- Originator company, and product brand name: Gilead/BMS/Merck, Atripla.
- First approval by U.S. Food and Drug Administration (FDA): July 2006.[19]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- 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.[20]
- World sales of the originator: In 2006, when the product entered the market in the third quarter of the year, sales reached US$205.7 million; in 2007, sales totaled US$903.4 million.[130]
- Most patents related to TDF, FTC, TDF/FTC or to EFV also affect this combination. In addition, Gilead and BMS jointly applied for patents specifically related to this combination in 2006[132], 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.

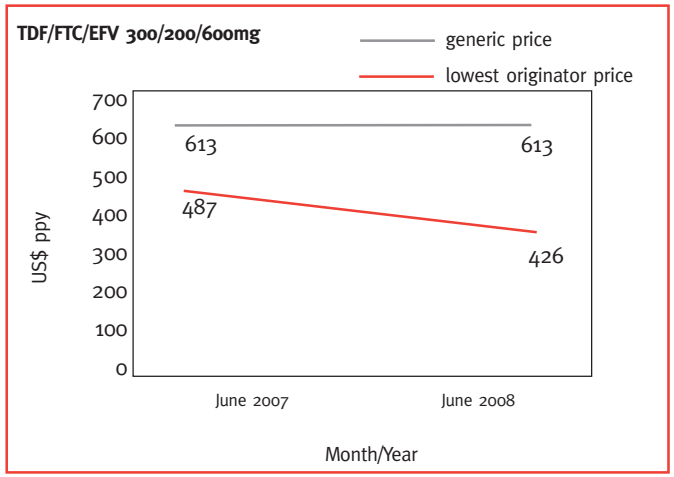
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Gilead/BMS/Merck		Matrix (CF)	Cipla
		Category 1	Category 2		
Eligibility restrictions		See Annex 10		None	None
TDF/FTC/EFV 300/200/600mg tablet	1	**613 (1.680)**	**1033 (2.830)**	426 (1.167)	633 (1.733)

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were no WHO prequalified generic sources of TDF/FTC/EFV. The lowest available generic price is therefore shown here.

TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/EFAVIRENZ (TDF/FTC/EFV) FIXED-DOSE COMBINATIONS & CO-PACKS

Spotlight on access issues:

The 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to less toxic AZT- or TDF-based regimens.[15] This combination is likely to be widely used in developing countries in first-line regimens in the future.

As a result of these changes, the use the TDF/FTC/EFV FDC is expected to increase, which will have a substantial impact on the budgets of HIV/AIDS treatment programmes. The previously-recommended d4T-based first-line regimens now cost less than US$100 per patient per year. Changing to a TDF-based first-line in a fixed-dose combination would increase the cost between four and elevenfold (see graphs 2 and 3). Although 3TC and FTC are clinically interchangeable, the price today of the 3TC is almost half that of FTC.

Today, there is no WHO prequalified generic triple FDC available.

Patents: This combination could be developed by Indian generic companies because none of the individual components are patented in India today. However, Gilead has applied for patents related to TDF, which are pending a decision from the Indian Patent Office. If these patents are granted in India, generic competition for this product may be affected. Following oppositions to its patent applications in India, Gilead signed licensing agreements with ten Indian generic manufacturers in September 2006 for the production of generic TDF and combinations containing TDF, in exchange for a 5% royalty. Gilead has stipulated in these licences a pre-defined list of countries to which companies can export. Not all countries and patients can therefore benefit from this competition. Additionally Gilead's licences limit the supply of Active Pharmaceutical Ingredients (API) by its licencees to pre-approved producers only.[87]

Paediatrics: TDF is not currently approved for children younger than 18 years.

General information

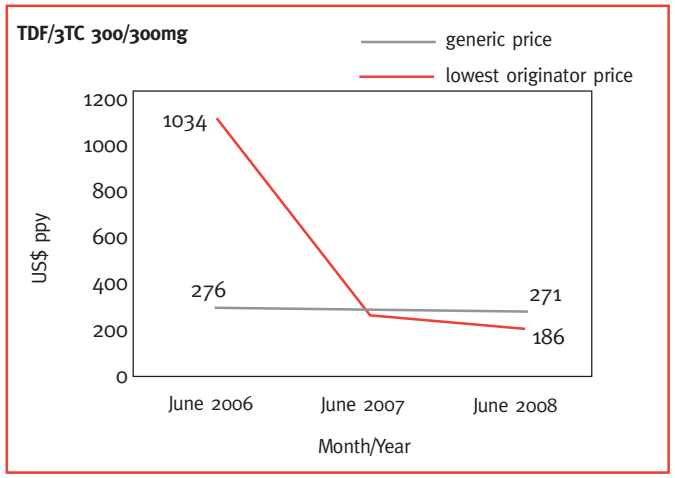
- Therapeutic class: NtRTI + NRTI in a double fixed-dose combination.
- Indicated for first-line, for adults and adolescents (2006 WHO guidelines).[15]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.[20]
- Most patents related to TDF or to 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. Cipla applied for patents more specifically related to this combination.[133]

For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Cipla (CF)	Matrix (CF)
Eligibility restrictions		None	None
TDF/3TC 300/300mg tablet	1	186 (0.509)	213 (0.583)

(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 eligible developing countries since 2006.

As of June 2008, there was no WHO prequalified product. The lowest available generic price is therefore shown in the graph.

As there is no originator FDC, the prices used are for the combination of the two single 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. The 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to less-toxic AZT- or TDF-based regimens.[15]

Additionally, in 2007, WHO convened a technical consultation to simplify the choice of second-line regimens, and has recommended TDF in combination with 3TC or FTC as one of the two recommended NRTI backbones (the second option being ABC/ddI) to be added to a boosted PI for patients whose initial regimen was 3TC/d4T/NVP.[57]

As a result of these changes, the use the TDF/3TC FDC is expected to increase, which will have a substantial impact on the budgets of HIV/AIDS treatment programmes. The previously-recommended d4T-based first-line regimens now cost less than US$100 per patient per year. Changing to a TDF-based first-line in a fixed-dose combination would increase the cost between four and elevenfold (see graphs 2 and 3). Although 3TC and FTC are clinically interchangeable, the price today of the 3TC is almost half that of FTC.

Today, there is no WHO prequalified generic double FDC available.

Patents: This combination could be developed by Indian generic companies because none of the individual components are patented in India today. However, Gilead has applied for patents related to TDF, which are pending a decision from the Indian Patent Office. If these patents are granted in India, generic competition for this product may be affected. Following oppositions to its patent applications in India, Gilead signed licensing agreements with ten Indian generic manufacturers in September 2006 for the production of generic TDF and combinations containing TDF, in exchange for a 5% royalty. Gilead has stipulated in these licences a pre-defined list of countries to which companies can export. Not all countries and patients can therefore benefit from this competition. Additionally Gilead's licences limit the supply of Active Pharmaceutical Ingredient (API) by its licensees to pre-approved producers only.[87]

Paediatrics: TDF is not currently approved for children younger than 18 years.

General information

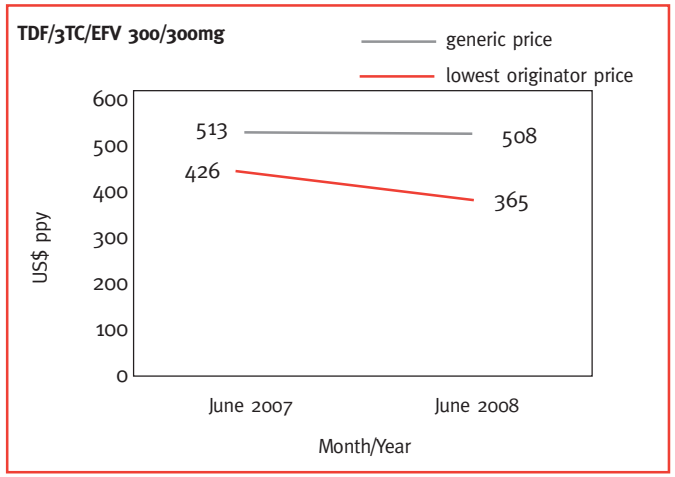
- Therapeutic class: one NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination or co-pack.
- Indicated for first-line for adults (WHO 2006 guidelines). [15]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.[20]
- Most patents related to TDF, 3TC or to 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.

For information on the individual ARVs contained in this fixed-dose combination and co-pack please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Cipla (CF)	Matrix (CF)
Eligibility restrictions		None	None
TDF/3TC/EFV 300/150/600mg tablet (FDC)	1		365 (1.000)
TDF/3TC 300/150 mg + EFV 600mg (Co-Pack)	1 kit (2 tabs)	350 (0.959)	

(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 eligible developing countries since 2006.

As of June 2008, there was no WHO prequalified product. The lowest available generic price is therefore shown in the graph.

As there is no originator FDC, the prices used are for the combination of the three single originator products.

Spotlight on access issues:

The 2006 WHO guidelines suggest countries start to consider moving away from d4T-based regimens to less toxic AZT- or TDF-based regimens.[15] This combination is likely to be widely used in developing countries in first-line regimens in the future. As a result of these changes, the use the TDF/3TC/EFV FDC is expected to increase, which will have a substantial impact on the budgets of HIV/AIDS treatment programmes. The previously-recommended d4T-based first-line regimens now cost less than US$100 per patient per year. Changing to a TDF-based first-line in a fixed-dose combination would increase the cost between four and elevenfold (see graphs 2 and 3). Although 3TC and FTC are clinically interchangeable, the price today of the 3TC is almost half that of FTC.

Today, there is no WHO prequalified triple FDC available.

Patents: This combination could be developed by Indian generic companies because none of the individual components are patented in India today. However, Gilead has applied for patents related to TDF, which are pending a decision from the Indian Patent Office. If these patents are granted in India, generic competition for this product may be affected. Following oppositions to its patent applications in India, Gilead signed licensing agreements with ten Indian generic manufacturers in September 2006 for the production of generic TDF and combinations containing TDF, in exchange for a 5% royalty. Gilead has stipulated in these licences a pre-defined list of countries to which companies can export. Additionally Gilead's licences limit the supply of Active Pharmaceutical Ingredient (API) by its licensees to pre-approved producers only.[87] Not all countries and patients can therefore benefit from this competition.

Paediatrics: TDF is not currently approved for children younger than 18 years.

General information

- Therapeutic class: two NRTIs in double fixed-dose combination.
- Indicated for first- and second-line for adults and adolescents, and only for first-line in children (WHO 2006 guidelines).[15,16]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Combivir.
- First approval by U.S. Food and Drug Administration (FDA): September 1997.[19]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- 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.[20]
- World sales of the originator: 2007: US$888 million; 2006: US$1,042 million; 2005: US$1,150 million; 2004: US$1,125 million.[58,59,60,61]
- Most patents related to AZT or to 3TC also affect this combination. In addition, GSK applied for patents specifically related to the use of AZT and 3TC in combination,[134] and for the tablet formulation of the FDC,[135] which are due to expire in 2012 and 2017, respectively.

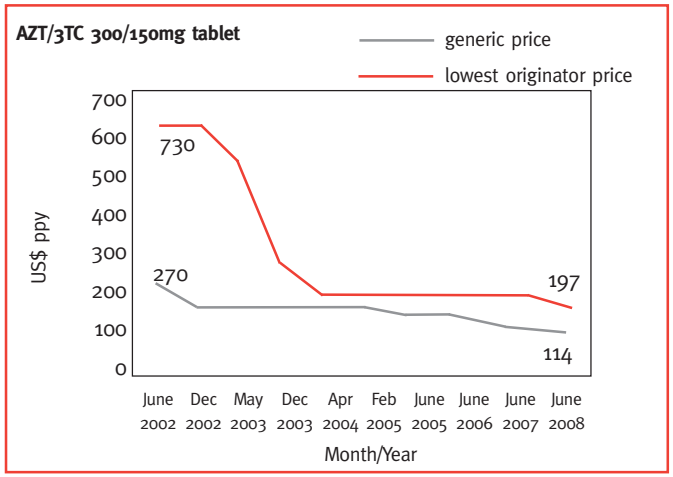
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Aurobindo	Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy	Strides
Eligibility restrictions		See Annex 2	None	None	None	None	None	None
AZT/3TC 300/150mg tablet	2	**197 (0.270)**	**128 (0.175)**	**114 (0.156)**	**129 (0.177)**	**128 (0.175)**	**140 (0.192)**	153 (0.210)
AZT/3TC 60/30mg tablet	4					121 (0.083)		

(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.

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were five WHO prequalified generic sources of AZT/3TC. The lowest available generic price is therefore 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 58% since 2001.

Spotlight on access issues:

There will be a continued need for this important FDC. The 2006 WHO treatment guidelines suggest countries start to consider moving away for d4T-based regimens to less toxic AZT- or TDF-based regimens.[15]

Additionally, in 2007, WHO convened a technical consultation to simplify the choice of second-line regimens, and AZT in combination with 3TC was the recommended NRTI backbone to be added to a boosted PI for patients whose initial regimen was a TDF-based.[57]

Patents: Generic versions of this combination were developed in countries where neither of the drugs, nor their combination, was patented. However, the generic versions of the medicine produced in India came under threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination. Civil society organisations in India opposed the patent application in March 2006,[43] which resulted in GSK communicating in August 2006 that patents specifically related to the FDC were being withdrawn in all countries.[136]

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$3,199 ppy.

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 minimize the side effects. For simplification, there is an urgent need for a quality-assured double FDC to allow children to be safely and accurately dosed while starting treatment. The alternative is to use two different syrups, which can be are difficult to administer. Today, there are no WHO prequalified AZT/3TC FDC tablets available. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric AZT/3TC FDC as an “urgent” priority.[17]

General information

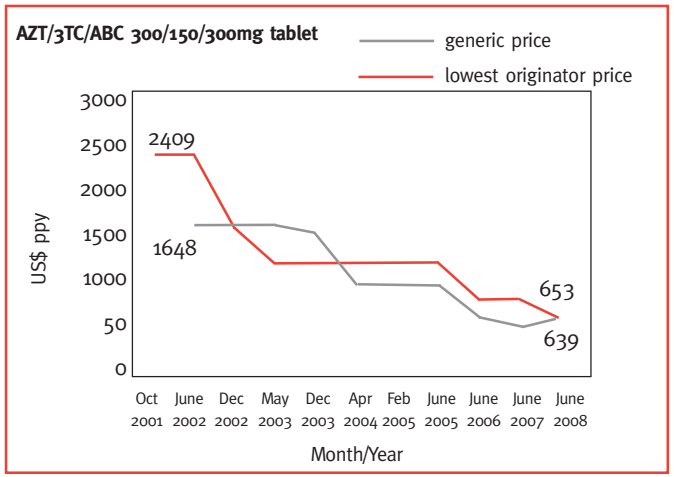
- Therapeutic class: three NRTIs in triple fixed-dose combination.
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.[20]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Trizivir.
- First approval by U.S. Food and Drug Administration (FDA): November 2000.[19]
- World sales of originator product: 2007: US$455 million; 2006: US$529 million; 2005: US$598 million; 2004: US$635 million.[58,59,60,61]
- Most patents on AZT, 3TC or ABC also affect this combination. In addition, GSK applied for patents more specifically related to the combination,[128] which are due to expire in 2016.

For information on the individual ARVs contained in this fixed-dose combination and co-pack please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	GSK	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy
Eligibility restrictions		See Annex 2	None	None	None	None	None
AZT/3TC/ABC 300/150/300mg tablet (FDC)	2	**653 (0.895)**		548 (0.750)	467 (0.640)	487 (0.667)	**639 (0.875)**
AZT/3TC 300/150 + ABC 300mg (Co-Pack)	1 kit (4 tabs)		**444 (1.217)**				

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there was one WHO prequalified generic source of the FDC of AZT/3TC/ABC. The lowest available generic price is therefore shown here.

There has been a decrease of 61% 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. It is one of the most commonly-prescribed regimens in the developed world, but the market is very small in developing countries. This combination at best costs more than four times what the most commonly-used FDC (3TC/d4T/NVP) costs today, this is predominately due to the high cost of ABC.

Patents: GSK could not apply for basic patents related to ABC, AZT or 3TC in some developing countries such as India, which did not grant patents on pharmaceuticals at the time. This allowed Indian generic companies to develop generic versions of each medicine, and of the combination. However, GSK widely applied for patents in other developing countries, where possible. In India, GSK had applied for patents more specifically related to the FDC. The company withdrew the patent application after a pre-grant opposition was filed in 2006.[137]

Paediatrics: For children who need this combination, the current option is three syrups. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric formulation of AZT/3TC/ABC FDC an “urgent” priority.[17]

General information

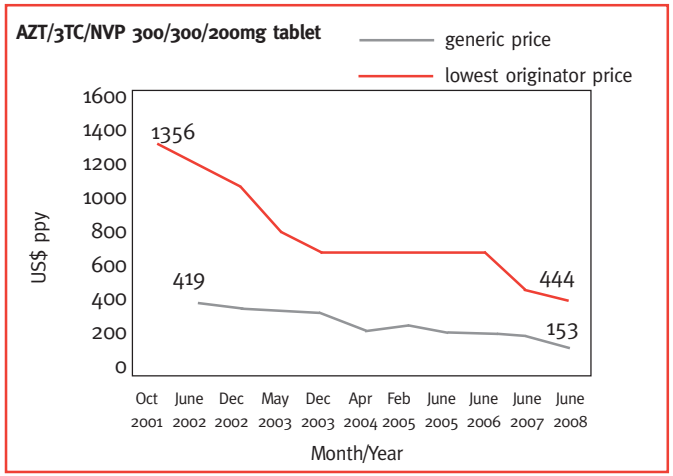
- Therapeutic class: two NRTI + one NNRTI in triple fixed-dose combination.
- Indicated for first-line, for adults, adolescents and children (WHO 2006 guidelines).[15,16]
- Included in the WHO Model List of Essential Medicines (EML).[20]
- The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.[20]
- Most patents related to AZT, 3TC, AZT/3TC or to 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.

For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy
Eligibility restrictions		None	None	None	None	None
AZT/3TC/NVP 300/150/200mg tablet	2	**167 (0.229)**	**153 (0.210)**	**166 (0.228)**	183 (0.250)	223 (0.306)
AZT/3TC/NVP 60/30/50mg tablet	4				158 (0.108)	
AZT/3TC/NVP 60/30/60mg dispersible tablet	--					(0.135)

(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.
Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.



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

As of June 2008, there were three WHO prequalified generic sources of the AZT/3TC/NVP FDC. The lowest available generic price is therefore shown here.

As there is no originator FDC, the prices used are for the combination of the three single products. Generic prices have steadily decrease by 63% since 2001.

Spotlight on access issues:

There will be a continued need for this important FDC. The 2006 WHO treatment guidelines suggest countries start to consider moving away from d4T-based regimens to less-toxic AZT- or TDF-based regimens.[15]

Patents: In addition to the generic manufacturers referenced above, Apotex also manufactures an AZT/3TC/NVP fixed-dose combination[138] for export to developing countries under the 30 August 2003 WTO decision on compulsory licensing for export.[139]

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.[140] 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. For simplification, there is an urgent need for a quality-assured triple FDC, to allow children to be safely and accurately dosed. The alternative today is to use three different syrups that can be difficult to administer. Today, there are no WHO prequalified AZT/3TC/NVP FDC tablets available. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric formulation of an AZT/3TC/NVP FDC as an "urgent" priority.[17]

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 (WHO 2006 guidelines).[15,16]
- 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.[20]
- Most patents related to AZT, 3TC, AZT/3TC or to EFV also affect this combination. In addition, Cipla applied for patents specifically related to the use of AZT, 3TC and EFV in combination.[141]

For information on the individual ARVs contained in this co-pack please refer to the individual drug product cards.

Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Aurobindo	Cipla	Ranbaxy
Eligibility restrictions		None	None	None
AZT/3TC +EFV 300/150 + 600mg daily co-pack	1 kit (3 tabs)	**313 (0.858)**	320 (0.877)	**434 (1.190)**

Products included in the most recent edition of the WHO List of Prequalified Medicines (as of 14 May 2008) are in **bold**.

Spotlight on access issues:

Patents: Basic patents related to AZT, 3TC or EFV could not be obtained in some developing countries such as India, which did not grant product patents on pharmaceuticals at the time. This allowed Indian drug companies to manufacture generic versions of the medicines and to develop this product. However, GSK and Merck may hold patents in other developing countries, which could prevent its importation and use.

Annex 1: Summary of prices in US$ quoted by companies for eligible developing countries

Prices are quoted as per patient year followed in brackets by the smallest unit price.

ABC	**Daily dose**	**Aurobindo**	**Cipla**	**GSK**	**Hetero**	**Matrix**	**Ranbaxy**		
300mg tablet	2	**321 (0.440)**	**334 (0.458)**	**437 (0.599)**	336 (0.460)	**365 (0.500)**	473 (0.648)		
20mg oral solution	10ml	**259 (0.071/ml)**	420 (0.115/ml)	**230 (0.063)**					
60mg tablet	4		160 (0.110)			194 (0.133)			
ATV		**BMS**							
		Cat 1	Cat 2						
150mg capsule	2	353 (0.484)	425 (0.582)						
200mg capsule	--	(0.602)	(0.732)						
ddI		**Aurobindo**	**BMS**		**Cipla**	**Hetero**	**Ranbaxy**		
			Cat 1	Cat 2					
25mg tablet	5		**212 (0.116)**	**429 (0.235)**	115 (0.063)				
50mg tablet	--		**(0.158)**	**(0.235)**	(0.079)				
100mg tablet	4	**219 (0.150)**	**310 (0.212)**	**364 (0.249)**	166 (0.114)	160 (0.110)	242 (0.166)		
150mg tablet	--	**(0.225)**	**(0.308)**	**(0.345)**	(0.167)				
200mg tablet	--	**(0.300)**	**(0.425)**		(0.232)				
125mg EC capsule	--	(0.186)							
250mg EC capsule	1	172 (0.471)	**223 (0.611)**	**247 (0.667)**	103 (0.283)	139 (0.380)	170 (0.466)		
400mg EC capsule	1	270 (0.740)	**288 (0.789)**	**319 (0.846)**	132 (0.363)	161 (0.440)	304 (0.832)		
2g powder for reconstitution	12ml	**88 (4.00/2g)**	**276 (12.59/2g)**	**305 (13.937/2g)**					
EFV		**Aurobindo**	**Cipla**	**Hetero**	**Matrix**	**Merck**		**Ranbaxy**	**Strides**
						Cat 1	Cat 2		
50mg capsule	--	**(0.092)**				**(0.120)**	**(0.210)**		
50mg tablet	--					**(0.120)**	**(0.210)**		
100mg capsule	--	**(0.483)**							
200mg capsule	3	**183 (0.167)**	186 (0.170)	153 (0.140)		**394 (0.360)**	**821 (0.750)**	**210 (0.192)**	186 (0.170)
200mg tablet	3					**394 (0.360**	**821 (0.750)**		
600mg tablet	1	**158 (0.432)**	**170 (0.467)**	146 (0.400)	**152 (0.417)**	**237 (0.650)**	**657 (1.800)**	**185 (0.506)**	**180 (0.500)**
30mg/ml suspension	--					**(0.094/ml)**	**(0.151/ml)**		
FPV		**GSK**							
700mg tablet	2	1222 (1.674)							
50mg/ml suspension	12ml	648 (0.148/ml)							

FTC	Daily dose	Hetero								
200mg capsule	1	66 (0.180)								
IDV		**Aurobindo**	**Cipla**	**Hetero**	**Merck**		**Ranbaxy**			
					Cat 1	Cat 2				
400mg capsule	4	365 (0.250)	422 (0.289)	**374 (0.256)**	**394 (0.270)**	**686 (0.470)**	381 (0.261)			
3TC		**Aurobindo**	**Cipla**	**GSK**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**		
150mg tablet	2	**40 (0.055)**	**35 (0.048)**	**64 (0.087)**	**37 (0.050)**	**42 (0.058)**	**43 (0.059)**	**52 (0.071)**		
300mg tablet	1	**24 (0.067)**	50 (0.137)							
10mg/ml suspension	10ml		**37 (0.010/ml)**	**84 (0.023/ml)**						
25mg granules	--							(2.200)		
50mg granules	--							(2.700)		
NFV		**Cipla**	**Hetero**	**Roche**						
				Cat 1	Cat 2					
250mg tablet	10	1113 (0.305)	1132 (0.310)	**1248 (0.342)**	**2562 (0.702)**					
50mg/g oral powder	24g			**2243 (0.256/g)**	**2593 (0.296/g)**					
NVP		**Aurobindo**	**Boehringer**		**Cipla**	**Hetero**	**Huahai**	**Matrix**	**Ranbaxy**	**Strides**
			Cat 1	Cat 2						
200mg tablet	2	**46 (0.063)**	**219 (0.300)**	**438 (0.600)**	**35 (0.048)**	**44 (0.060)**	**46 (0.063)**	52 (0.071)	**51 (0.070)**	**58 (0.080)**
10mg/ml suspension	20ml	**66 (0.009/ml)**	**380 (0.052/ml)**	**533 (0.073/ml)**	73 (0.010/ml)					
25mg granules	--									(2.500)
50mg granules	--									(3.000)
RTV		**Abbott**	**Cipla**	**Hetero**	**Strides**					
100mg capsule	2	**83 (0.114)**	313 (0.429)	197 (0.270)	365 (0.500)					
80mg/ml oral solution	--	**(0.093/ml)**								
SQV		**Cipla**	**Hetero**	**Roche**						
				Cat 1	Cat 2					
200mg hard-capsule	10	1825 (0.500)		**1223 (0.335)**	**2562 (0.702)**					
500mg tablet	4		1533 (1.050)	**1127 (0.772)**	**2559 (1.753)**					
d4T		**Aurobindo**	**BMS**		**Cipla**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**	
			Cat 1	Cat 2						
15mg capsule	--	**(0.029)**	**(0.082)**	**(0.093)**	(0.025)	(0.022)				
20mg capsule	--	**(0.030)**	**(0.089)**	**(0.092)**	(0.023)	(0.025)				
30mg capsule	2	**23 (0.032)**	**48 (0.066)**	**67 (0.092)**	19 (0.026)	22 (0.030)	**24 (0.033)**	**28 (0.039)**	**27 (0.037)**	
40mg capsule	2	**28 (0.038)**	**55 (0.075)**	**67 (0.092)**		26 (0.036)	**31 (0.042)**	**34 (0.047)**	**30 (0.042)**	
1mg powder for suspension	20ml	**66 (0.009/ml)**	**51 (0.007/ml)**	**58 (0.008/ml)**	44 (0.006/ml)					
5mg granules	--								(2.000)	
10mg granules	--								(2.500)	

TDF	Daily Dose	Cipla	Gilead		Hetero	Matrix	Ranbaxy		
			Cat 1	Cat 2					
300mg tablet	1	151 (0.415)	**207 (0.567)**	**365 (1.000)**	128 (0.350)	**158 (0.433)**	194 (0.532)		
AZT		**Aurobindo**	**Cipla**	**GSK**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**	
300mg tablet	2	**110 (0.150)**	**107 (0.146)**	**161 (0.221)**	99 (0.135)	104 (0.142)	**115 (0.157)**		
100mg capsule	--	**(0.100)**	**(0.050)**	**(0.122)**					
250mg capsule	--			**(0.276)**					
10mg/ml suspension	20ml	**73 (0.010/ml)**	**73 (0.010)**	**234 (0.032)**					
25mg granules	--							(2.850)	
50mg granules	--							(3.350)	
ABC/3TC		**Cipla**	**GSK**	**Matrix**					
600/300mg tablet	1	243 (0.667)	484 (1.326)						
60/30mg tablet	4			219 (0.150)					
3TC/d4T		**Aurobindo**	**Cipla**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**		
150/30mg tablet	2	53 (0.072)	**52 (0.071)**	46 (0.063)	55 (0.075)	**61 (0.083)**	52 (0.071)		
150/40mg tablet	2	55 (0.075)		52 (0.071)	61 (0.083)	**64 (0.088)**	**55 (0.075)**		
30/6mg dispersible tablet	4		51 (0.035)						
60/12mg dispersible tablet	2		50 (0.068)						
20/5mg dispersible tablet	--					(0.038)			
40/10mg dispersible tablet	--					(0.053)			
LPV/r		**Abbott**		**Aurobindo**	**Cipla**	**Hetero**	**Matrix**		
		Cat 1	Cat 2						
133/33mg soft-gel capsule	6	**500 (0.228)**	**1000 (0.457)**		1338 (0.611)	447 (0.204)			
200/50mg tablet (heat-stable)	4	**500 (0.342)**	**1000 (0.457)**	768 (0.526)	1339 (0.917)		705 (0.483)		
80/20mg solution	4ml	**200 (0.137/ml)**	**400 (0.274/ml)**						
100/25mg tablet (heat-stable)	2	125 (0.171)	250 (0.343)	293 (0.401)			204 (0.279)		
TDF/FTC		**Cipla**	**Gilead**		**Hetero**	**Matrix**			
			Cat 1	Cat 2					
300/200mg tablet	1	240 (0.658)	**319 (0.875)**	**548 (1.500)**	215 (0.590)	243 (0.667)			
TDF/3TC		**Cipla**	**Matrix**						
300/300mg tablet	1	186 (0.509)	213 (0.583)						
AZT/3TC		**Aurobindo**	**Cipla**	**GSK**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**	
300/150mg tablet	2	**128 (0.175)**	**114 (0.156)**	**197 (0.270)**	**129 (0.177)**	**128 (0.175)**	**140 (0.192)**	1153 (0.210)	
60/30mg tablet	4					121 (0.083)			

3Tc/d4T/NVP		**Aurobindo**	**Cipla**	**Hetero**	**Matrix**	**Ranbaxy**	**Strides**		
30/6/50mg dispersible tablet	4		**117 (0.080)**	55 (0.038)					
60/12/100mg dispersible tablet	2		**61 (0.084)**	46 (0.063)					
20/5/35mg dispersible tablet	--					(0.054)			
40/10/70mg dispersible tablet	--					(0.092)			
150/30/200mg tablet	2	82 (0.113)	**96 (0.132)**	**87 (0.119)**	104 (0.142)	**99 (0.135)**	102 (0.140)		
150/40/200mg tablet	2			**97 (0.125)**	110 (0.175)	**101 (0.139)**	106 (0.145)		
TDF/FTC/EFV		**Cipla**	**Matrix**	**BMS/Gilead/Merck**					
				See Annex 10					
300/200/600mg tablet	1	633 (1.733)	426 (1.167)	**613 (1.680)**	**1033 (2.830)**				
TDF/3TC/EFV		**Cipla**	**Matrix**						
300/300/600mg tablet (FDC)	1		365 (1.000)						
300/300 + 600mg (Co-pack)	1 kit (2 tabs)	350 (0.959)							
AZT/3TC/ABC		**Aurobindo**	**Cipla**	**GSK**	**Hetero**	**Matrix**	**Ranbaxy**		
300/150/300mg tablet (FDC)	2		548 (0.750)	**653 (0.895)**	467 (0.640)	487 (0.667)	**639 (0.875)**		
300/150 + 300mg (Co-pack)	1 kit (4 tabs)	**444 (1.217)**							
AZT/3TC/NVP		**Aurobindo**	**Cipla**	**Hetero**	**Matrix**	**Ranbaxy**			
300/150/200mg tablet	2	**167 (0.229)**	**153 (0.210)**	**166 (0.228)**	183 (0.250)	223 (0.306)			
60/30/50mg tablet	4				158 (0.108)				
60/30/60mg dispersible tablet	--					(0.135)			
3TC/d4T + EFV (Co-pack)		**Cipla**	**Ranbaxy**	**Strides**					
150/30 + 600mg	1 kit (3 tabs)	274 (0.750)	345 (0.945)						
150/40 + 600mg	1 kit (3 tabs)		358 (0.980)	234 (0.641)					
AZT/3TC + EFV (Co-pack)		**Aurobindo**	**Cipla**	**Ranbaxy**					
150/300 + 600mg	1 kit (3 tabs)	**313 (0.858)**	320 (0.877)	**434 (1.190)**					
NVP + AZT (Co-pack)		**Strides**							
6 + 16mg granules	1 + 14	(2.500)							
6 + 16mg granules	1 + 56	(4.700)							

Annex 2: Conditions of offer by company

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
Abbott	Category 1 countries: All African countries and all United Nations defined least developed countries outside Africa. Category 2 countries: See Annex 8 for more details.	Governments and programmes fully funded by governments, UN systems organisations, NGOs and other not-for-profit institutional providers in low and low-middle-income countries.		FOB.
Aurobindo	No reported restrictions.	NGOs and governmental organisations.	FOB prices, freight & insurance extra as per country & mode - Air or Sea. Prices available for above 300,000 units for tablet packs and above 3,000 packs for oral solutions. Delivery of goods 4-6 weeks from the date of confirmed orders.	Payment by letter of credit or Advance payment. FOB Hyderabad (India).
Bristol-Myers Squibb	First category of 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). Second category of countries: Southern African countries See Annex 7 for more details. For other developing countries, prices are negotiated on a case-by-case basis with BMS local representatives.	Both private and public sector organisations that are able to provide effective, sustainable and medically-sound care and treatment of HIV/AIDS.	Category 1 countries are invoiced in US$. Category 2 countries are invoiced in South African Rand.	CIP incoterm.
Boehringer Ingelheim	Category 1: All LDCs, all low income countries and all of Africa. Category 2: All middle-income countries not covered under category 1.	Governments, NGOs and other partners who can guarantee that the programme is run in a responsible manner.	CIP.	CIP.
Cipla	No reported restrictions but higher prices have been negotiated separately for ten Latin American countries.	No restrictions.	No quantity-related conditions. Prices for larger quantities are negotiable.	FOB Mumbai (India) or CIF - The actual freight charges are charged separately.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
Gilead	Over 125 countries are eligible, including all African countries and additional countries classified as low- or lower-middle-income by the World Bank. See Annex 9 for more details. For other developing countries, prices are negotiated on a case-by-case basis.	Organisations that provide HIV treatment in the more than 125 countries are covered by the Gilead Access Program. For organisations in Africa enquiries should be directed to Jennifer Watt: jwatt@gilead.com or +44 20 8587 2228. All other enquiries should be directed to Access@gilead.com or via telephone at +1 650 522 5101. Additional information is available at: www.gilead.com.	The programme is managed through Gilead 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.
GlaxoSmithKline	Least Developed Countries (LDCs) plus sub-Saharan Africa. 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. 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.	Governments, aid organisations, charities, UN agencies, other not-for-profit organisations and international procurement agencies. In sub-Saharan Africa, employers offering HIV/AIDS care and treatment directly to their uninsured staff through workplace clinics or similar arrangements.	Supply Agreement required (for NGOs requiring fewer than ten patient packs per month, this requirement may be waived). All organisations must supply the preferentially priced products on a not-for-profit basis.	CIP.
Hetero Drugs	No reported restrictions.	Private sector, public sector and NGOs.	Prices may be negotiated on individual basis according commercial terms.	FOB Mumbai (India).
Matrix	No reported restrictions except Belarus, Cuba, Democratic Republic of Congo, Iran, Liberia, Sudan and Syria for which prior approval from Mylan Labs Inc is required.	No restrictions.	None.	Ex-works Nashik, India or as specified by customers.
Merck & Co.	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 & Co. Inc may under certain circumstances supply ARVs to patients through retail pharmacies.	CIP.
Ranbaxy	No reported restrictions, but higher prices were negotiated separately for ten Latin American countries.	NGOs and governments or programmes supported by them.	Confirmed letter of credit or advance payment preferred for new customers.	FCA Delhi (India).

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
Roche	First category of countries: All countries in sub-Saharan Africa and all countries classified as Least Developed Countries by the United Nations. Second category of countries: Low-income countries and lower middle-income countries, as classified by the World Bank.	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).

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 instance, 25 countries are considered Least Developed Countries (LDCs) by the United Nations, but are classified as having medium development by UNDP Human Development Index (HDI). These include countries such as Bangladesh, Cambodia, Laos, Haiti, Uganda and Sudan. Seven other LDCs do not appear in the UNDP HDI rankings at all. These include Liberia and Somalia.

For complete details please refer to Annexes 3-10.

Annex 3: Least Developed Countries (LDCs)

Source: United Nations
http://www.un.org/special-rep/ohrlls/ldc/list.htm

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

Afghanistan; Angola; Bangladesh; Benin; Bhutan; Burkina Faso; Burundi; Cambodia; Cape Verde; Central African Republic; Chad; Comoros; Congo (Democratic Republic); 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 Principe; Senegal; Sierra Leone; Solomon Islands; Somalia; Sudan; Timor-Leste; Togo; Tuvalu; Uganda; Tanzania; 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:
Angola; Benin; Burkina Faso; Burundi;, Central African Republic; Chad; Congo (Democratic Republic); Côte d'Ivoire; Eritrea; Ethiopia; Guinea; Guinea-Bissau; Malawi; Mali; Mozambique; Niger; Nigeria; Rwanda; Senegal; Sierra Leone; Tanzania; Zambia.

Medium human development:
Algeria; Armenia; Azerbaijan; Bangladesh; Belize; Bhutan; Bolivia; Botswana; Cambodia; Cameroon; Cape Verde; China; Colombia; Comoros; Congo; Djibouti; Dominica; Dominican Republic; Ecuador; Egypt; El Salvador; Equatorial Guinea; Fiji; Gabon; Gambia; Georgia; Ghana; Grenada; Guatemala; Guyana; Haiti; Honduras; India; Indonesia; Iran; Jamaica; Jordan; Kazakhstan; Kenya; Kyrgyzstan; Lao PDR; Lebanon; Lesotho; Madagascar; Maldives; Mauritania; Moldova; Mongolia; Morocco; Myanmar; Namibia; Nepal; Nicaragua; Pakistan; Palestinian Territories; Papua New Guinea; Paraguay; Peru; Philippines; St. Lucia; St. Vincent and the Grenadines; Samoa; São Tomé and Principe; Solomon Islands; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syrian Arab Republic; Tajikistan; Thailand; Timor-Leste; Togo; Tunisia; Turkey; Turkmenistan; Uganda; Ukraine; Uzbekistan; Vanuatu; Venezuela; Vietnam; Yemen; Zimbabwe.

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 (Democratic Republic); Côte d'Ivoire; Equatorial Guinea; 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 Principe; 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 effective from 1 July 2008.

Low-income economies:
Afghanistan; Bangladesh; Benin; Burkina Faso; Burundi; Cambodia; Central African Republic; Chad; Comoros; Congo (Democratic Republic); Côte d'Ivoire; Eritrea; Ethiopia; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Korea (Democratic Republic); Kyrgyzstan; Lao PDR; Liberia; Madagascar; Malawi; Mali; Mauritania; Mozambique; Myanmar; Nepal; Niger; Nigeria; Pakistan; Papua New Guinea; Rwanda; São Tomé and Principe; Senegal; Sierra Leone; Solomon Islands; Somalia; Tajikistan; Tanzania; Togo; Uganda; Uzbekistan; Vietnam; Yemen; Zambia; Zimbabwe.

Lower middle-income economies:
Albania; Algeria; Angola; Armenia; Azerbaijan; Bhutan; Bolivia; Bosnia and Herzegovina; Cameroon; Cape Verde; China; Colombia; Congo; Djibouti; Dominican Republic; Ecuador; Egypt; El Salvador; Georgia; Guatemala; Guyana; Honduras; India; Indonesia; Iran; Iraq; Jordan; Kiribati; Lesotho; Macedonia; Maldives; Marshall Islands; Micronesia; Moldova; Mongolia; Morocco; Namibia; Nicaragua; Paraguay; Peru; Philippines; Samoa; Sri Lanka; Sudan; Suriname; Swaziland; Syria; Thailand; Timor-Leste; Tonga; Tunisia; Turkmenistan; Ukraine; Vanuatu; West Bank and Gaza.

Upper middle-income economies:
American Samoa; Argentina; Belarus; Belize; Botswana; Brazil; Bulgaria; Chile; Costa Rica; Croatia; Cuba; Dominica; Fiji; Gabon; Grenada; Jamaica; Kazakhstan; Latvia; Lebanon; Libya; Lithuania; Malaysia; Mauritius; Mayotte; Mexico; Palau; Panama; Poland; Romania; Russian Federation; Serbia and Montenegro; Seychelles; South Africa; St. Kitts and Nevis; St. Lucia; St. Vincent and the Grenadines; Suriname; Turkey; Uruguay; Venezuela.

Annex 7: Bristol-Myers Squibb eligible countries

Category 1 Countries:
Afghanistan; Angola; Bangladesh; Benin; Bhutan; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; India; Kenya; Lao PDR; Liberia; Madagascar; Mali; Mauritania; Mauritius; Mongolia; Myanmar; Nepal; Nicaragua; Niger; Nigeria; Pakistan; Papua New Guinea; Rwanda; São Tomé and Principe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; Sudan; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Viet Nam; Yemen.

Category 2 Countries: Southern African countries
Botswana; Lesotho; Malawi; Mozambique; Namibia; South Africa; Swaziland; Zambia; Zimbabwe.

Annex 8: Abbott eligible countries

Source: Abbott's Access to HIV Care Program
http://www.abbott.com/static/content/document/aids_care.pdf

Category 1 Countries: Africa and Least developed countries
Afghanistan; Algeria; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo-Brazzaville; Côte d'Ivoire; Dem Rep of Congo; Djibouti; East Timor; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kiribati; Kenya; Laos; Lesotho; Liberia; Libya; Madagascar; Malawi; Maldives; Mali; Mauritania; Mauritius; Morocco; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Rwanda; Samoa; São Tomé and Principe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Swaziland; Tanzania; Togo; Tunisia; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.

Category 2 Countries: Low Income economies (excluding Africa and the LDC as defined by the UN)
India; Kyrgyzstan; Mongolia; Pakistan; Papua New Guinea; Tajikistan; Uzbekistan; Vietnam.

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; Marshall Islands; Micronesia; Moldova; Nicaragua; Paraguay; Peru; Philippines; Serbia and Montenegro; Sri Lanka; Suriname; Syria; Thailand; The FYR-Macedonia; Tonga; Turkmenistan; Ukraine.

Annex 9: Gilead eligible countries

Source: Gilead Access Program
http://www.gilead.com

Category 1 Countries: Low-Income Pricing Tier
Afghanistan; Algeria; Angola; Anguilla; Antigua and Barbuda; Bahamas; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; British Virgin Islands; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo, Dem. Rep. of; 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, People's Dem. Rep.; Lesotho; Liberia; Libya; Madagascar; Malawi; Maldives; Mali; Mauritania; Mauritius; Moldova, Mongolia; Montserrat; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Pakistan; Palau; Panama; Papua New Guinea; Rwanda; St. Kitts and Nevis; St. Lucia ; St. Vincent and the Grenadines; Samoa; São Tomé and Principe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Suriname; Swaziland; Syria; Tajikistan; Tanzania, Timor-Leste; Togo; Trinidad and Tobago; Tunisia; Turks and Caicos; Tuvalu; Uganda; Ukraine; Uzbekistan; Vanuatu; Vietnam; Yemen; Zambia; Zimbabwe.

Category 2 Countries: Lower Middle-Income Pricing Tier
Albania; Armenia; Azerbaijan; Belarus; Bosnia and Herzegovina; China; Ecuador; El Salvador; Fiji; Georgia; Iran; Iraq; Jordan; Kazakhstan; Montenegro; Paraguay; Peru; Philippines; Serbia; Sri Lanka; Thailand; Tonga; Turkmenistan.

Annex 10: Merck & Co. eligible countries

Source: Merck & Co. correspondence

Merck's Pricing Policy for efavirenz and indinavir

Category 1 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 (Brazaville); Congo DRC, Dem. Côte d'Ivoire; Djibouti; Dominica; Dominican Republic; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Grenada; Guatemala; Guinea-Bissau; Guinea-Conakry; Guyana; Haiti; Honduras; Jamaica; Kenya; Kiribati; Lao, People's Dem. Rep.; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Moldova, Rep. of; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Pakistan; Panama; Papua New Guinea; Romania**; Russia; Rwanda; São Tomé and Principe; Senegal; Sierra Leone; Solomon Islands; Somalia; South Africa; St. Kitts and Nevis; St. Lucia; St. Vincent/Grenadines; Sudan; Suriname; Swaziland; Tanzania; Thailand;Timor-Leste; Togo; Trinidad and Tobago; Tuvalu; Uganda; Ukraine; Vanuatu; Western Samoa; Yemen; Zambia; Zimbabwe.

Category 2 Countries:
Albania; Algeria; Armenia; Azerbaijan; Belarus; Bolivia; Bosnia and Herzegovina; Brazil; Bulgaria; China; Colombia; Costa Rica; Ecuador; Egypt; El Salvador; Estonia; Fiji; Georgia; India; Indonesia; Iran; Jordan; Kazakhstan; Kyrgyzstan; Latvia; Lebanon; Libyan Ar. Jamahiriya; Lithuania; Macedonia; Malaysia; Mauritius; Mexico; Mongolia; Morocco; Nicaragua; Oman; Palestinian Teritories; Paraguay; Peru; Philippines; Saudi Arabia; Seychelles; Sri Lanka; Syrian Arab Rep.; Tajikistan; Tunisia; Turkey; Turkmenistan; Uzbekistan; Venezuela; Viet Nam.

NOTES:
1. Both the UNCTAD and UNDP HDI lists are the most current. UNCTAD list was most recently updated and published in June 2007. UNDP HDI was last updated and published in November 2007.
2. In Botswana, Merck donates (provides free of charge) Crixivan and Stocrin.
3. ** Due to a special partnership in Romania, Merck provides Crixivan and Stocrin in that country at a price at which we make no profit.
4. The following countries are neither on the UNCTAD LDC list nor located in sub-Saharan Africa. They have not been given a country classification (low, medium or high) by the UNDP. Enquiries about pricing for these countries will be handled on a case-by-case basis. They are Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

Merck's Pricing Policy for raltegravir

Category 1 Countries:
Afghanistan; Angola; Bangladesh; Benin; Bhutan; Botswana*; Burkina Faso; Burundi; Cambodia; Cameroon*; Cape Verde; Central

African Republic; Chad; Comoros; Congo (Brazzaville)*; Congo DRC; Côte d'Ivoire*; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gabon*; Gambia; Ghana*; Guinea-Bissau; Guinea-Conakry; Haiti; Kenya*; Kiribati; Lao, People's Dem. Rep.; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Mozambique; Myanmar; Namibia*; Nepal; Niger; Nigeria*; Rwanda; São Tomé and Principe; Senegal; Sierra Leone; Solomon Islands; Somalia; South Africa*; Sudan; Swaziland*; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vanuatu; Western Samoa; Yemen; Zambia; Zimbabwe*.

Category 2 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 (Rep. of); Mongolia; Morocco; Nicaragua; Pakistan; Palestinian Territories; Peru; Philippines; St. Lucia; St. Vincent/Grenadines; Sri Lanka; Suriname; Syrian Arab Rep.; Tajikistan; Thailand; Tunisia; Turkey; Turkmenistan; Ukraine; Uzbekistan; Venezuela; Viet Nam.

NOTES:
1. Both the UNCTAD and UNDP HDI lists are the most current. UNCTAD list was most recently updated and published in June 2007. UNDP HDI was last updated and published in November 2007.
2. *Countries in sub-Saharan Africa not on the UNCTAD list of Least Developed Countries (LDC) but whose public sectors are eligible for Tier I pricing. In Botswana, Merck donates (provides free of charge) Isentress.
3. **Receives significant reduced pricing due to extraordinary commitment in treating HIV/AIDS patients.
4. The following countries are neither on the UNCTAD LDC list nor located in sub-Saharan Africa. They have not been given a country classification (low, medium or high) by the UNDP. Inquiries about pricing for these countries will be handled on a case-by-case basis. They are Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

Merck's Pricing Category for TDF/FTC/EFV 300/200/600mg

Category 1 Countries:
Afghanistan; Angola; Antigua and Barbuda; Bangladesh; Belize; Benin; Bhutan; Botswana*; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo (Brazzaville); Congo DRC; Dem. Côte d'Ivoire; Djibouti; Dominica; Dominican Republic; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Grenada; Guatemala; Guinea-Bissau; Guinea-Conakry; Guyana; Haiti; Honduras; Jamaica; Kenya; Kiribati; Lao, People's Dem. Rep.; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Moldova (Rep. of); Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Pakistan; Panama; Papua New Guinea; Rwanda; São Tomé and Principe; Senegal; Sierra Leone; Solomon Islands; Somalia; South Africa; St. Kitts and Nevis; St. Lucia; St. Vincent/ Grenadines; Sudan; Suriname; Swaziland; Tanzania;Timor-Leste; Togo; Trinidad and Tobago; Tuvalu; Uganda; Ukraine; Vanuatu; Western Samoa; Yemen; Zambia; Zimbabwe.

Category 2 Countries:
Bolivia; Indonesia; Kyrgyzstan; Mauritius; Mongolia; Nicaragua; Seychelles; Syrian Arab Rep.; Tajikistan; Uzbekistan; Viet Nam.

NOTES:
1. Both the UNCTAD and UNDP HDI lists are the most current. UNCTAD list was most recently updated and published in June 2007. UNDP HDI was last updated and published in November 2007.
2. In Botswana, Merck donates (provides free of charge) Atripla.
3. The following countries are neither on the UNCTAD LDC list nor located in sub-Saharan Africa. They have not been given a country classification (low, medium or high) by the UNDP. Enquiries about pricing for these countries will be handled on a case-by-case basis. They are Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

Annex 11: Suggested resources for further information:

For documentation on prices:

- Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS (June 2005) http://www.who.int/medicines/areas/access/med_prices_hiv_aids/en/index.html
- Clinton Foundation antiretroviral price list http://www.clintonfoundation.org/pdf/chai-arv-price-list-050807.pdf
- WHO Global Price Reporting Mechanism http://www.who.int/3by5/amds/price/hdd/
- The Global Fund Price Reporting Mechanism http://www.theglobalfund.org/en/funds_raised/price_reporting/default.asp
- U.S. Government Accountability Office - 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
- Management Sciences for Health International Drug Price Indicator Guide http://erc.msh.org/
- WHO AFRO Region Essential Medicines Price Indicator, 2003 http://www.who.int/medicines/publications/afro-essential_med_price_indicator_nocover.pdf
- International Dispensary Association Price Indicator http://www.idafoundation.org/documents/ida_hiv_aids_aug_07_zondersnijlijnen.pdf

For documentation on patents, compulsory licences and other access issues:

- "Determining the patent status of essential medicines in developing countries", Health Economies and Drugs, EDM Series No. 17, UNAIDS/WHO/MSF, 2004. http://mednet2.who.int/sourcesprices/DeterminingEssMedPatentStatusW_Depliant.pdf
- HIV/AIDS Medicines and Related supplies: Contemporary context and procurement. Technical guide. Chapter 2 and Annex B. World Bank, Washington, D.C., 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. www.msfaccess.org
- Knowledge Ecology International http://www.keionline.org, or http://www.cptech.org/ip/health/
- An overview of health-related compulsory licences, Consumer Project on Technology http://www.cptech.org/ip/health/cl/recent-examples.html
- Neither expeditious, nor a solution - WTO August 30 Decision is Unworkable. An illustration through Canada's Jean Chrétien Pledge to Africa. www.msfaccess.org
- TRIPS, Pharmaceutical Patents and Access to Essential Medicines - Seattle, Doha and Beyond. 't Hoen, E. http://www.accessmed-msf.org/resources/key-publications/key-publication-detail/article/trips-pharmaceutical-patents-and-access-to-essential-medicines-seattle-doha-and-beyond/
- Economics of AIDS and Access to HIV/AIDS Care in Developing Countries, Issues and Challenges. ANRS, Collection Sciences socials et SIDA; 2003 pp39-67
- The Secretariat on Public Health, Innovation and Intellectual Property (PHI) http://www.who.int/phi/en/
- Report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) http://www.who.int/intellectualproperty/report/en/index.html
- Facts and Evidences on the 10 Burning Issues Related to the Government Use of Patents on three Patented Essential Drugs in Thailand. The Ministry of Public Health and The National Health Security Office Thailand February 2007. http://www.moph.go.th/hot/White%20Paper%20CL-EN.pdf
- The 10 burning questions on the Government Use of Patents on the four anti-cancer drugs in Thailand By The Ministry of Public Health And The National Health Security Office Thailand. February 2008. http://www.moph.go.th/hot/Second_white_paper_on_the_Thai_CL_%5bEN%5d.pdf
- Sustaining access to antiretroviral therapy in developing countries: lessons from Brazil and Thailand. Nathan Ford, David Wilson, Gabriela Costa Chaves, Michel Lotrowska and Kannikar Kijtiwatchakul. AIDS 2007, 21 (suppl 4):S21-S29. www.msfaccess.org
- Examples of the Importance of India as 'Pharmacy for the Developing World'. MSF Access Campaign, http://www.accessmed-msf.org/resources/key-publications/key-publication-detail/article/examples-of-the-importance-of-india-as-the-pharmacy-for-the-developing-world/
- U.S. Food and Drug Administration Orange Book http://www.fda.gov/cder/ob/
- The Regulatory status of Antiretroviral Drugs Database (WHO) http://ftp.who.int/htm/AMDS/drugsdatabase.pdf

For documentation on quality:

- World Health Organization (WHO) list of Prequalified Medicinal Products http://mednet3.who.int/prequal/
- U.S. Food and Drug Administration (FDA) Tentative Approvals http://www.fda.gov/cder/ogd/approvals/
- Catalogue of U.S. FDA Approved Drug Products http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
- FDA Approved Drug Products http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

For HIV Guidelines:

- WHO Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
- Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a public health approach 2007. http://www.who.int/hiv/pub/guidelines/paediatrico20907.pdf
- Preferred Antiretroviral Medicines for Treating and Preventing HIV Infection in Younger Children. Report of the WHO Paediatric Working Group http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
- Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach; Report of a WHO Working Group Meeting, Geneva, Switzerland, 21-22 May 2007. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf.
- Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting 10-11 April 2008, WHO. http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf

Other useful websites referenced in this document:

- UNICEF Procurement of HIV/AIDS Related Supplies. September 2007. 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
- WHO Model List of Essential Medicines. 15th edition - March 2007. http://www.who.int/medicines/publications/EssMedList15.pdf
- Van Roey J., von Schoen-Angerer T., Ford N., Calmy A. (2008), How developing world concerns need to be part of drug development plans: a case study of four emerging antiretrovirals. Drug Discovery Today, Vol.13,

www.msfaccess.org

Please check MSF Access Campaign's website for updates to, as well as back issues of, the publication Untangling the Web of ARV Price Reductions, for other MSF reports, and for all the latest news about patents, price, access to medicines, medical innovation, and for information on MSF's HIV/AIDS and other field programmes.

Annex 12: Company contacts

Abbott:
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Annex 13: The Clinton Foundation ARV list

CLINTON FOUNDATION

ANTIRETROVIRAL (ARV) PRICE LIST

The Clinton Foundation HIV/AIDS 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, Zhejiang Huahai Pharmaceutical Co., Matrix Laboratories, Ranbaxy Laboratories and Strides Arcolab. The ARVs included in CHAI's pricing agreements are: abacavir (ABC), didanosine (DDI), 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 69 nations. These prices apply to procurements using funding from local governments, the Global Fund and/or UNITAID which are conducted to support public care and treatment programs. Products should be purchased directly from partner suppliers or through procurement agents representing the aforementioned programs and funding sources. For all products containing TDF, prices offered by Matrix are available only to countries covered under the Gilead Voluntary License. To enquire about a particular country's eligibility for the Matrix TDF product prices, please contact Rikha Rani at rrani@clintonfoundation.org. 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. Certain products—including LPV/r (200/50mg), TDF (300mg) and select pediatric solutions—have two separate price ceilings that apply to different suppliers. CHAI expects that prices for these products will converge in the long term, and has elected to establish more than one price ceiling for the same product in a limited number of cases to balance the goals of offering the lowest possible 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. Prices per year for pediatric formulations assume a 10 kg child.

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) or a stringent regulatory authority such as the U.S. FDA. In the list below, footnotes specify the applicable quality assurance status for each formulation: (1) Approved by the WHO Prequalification Programme; (2) Approved by the U.S FDA or other stringent regulatory authority; (3) Submitted to the WHO, U.S. FDA or other stringent regulatory authority for review; (4) Expecting imminent submission to the WHO and/or FDA and already manufactured at a facility compliant with Good Manufacturing Practice (GMP).

ADULT PRODUCT		CEILING PRICE			SUPPLIER						
Name and strength	Packaging	Per year	Per pack	Per pill	Cipla	Hetero	Matrix	Ranbaxy	Aurobindo	Hunhai	Strides
ABC (300mg)	HDPE bottle 60 tablets	$300	$25.00	$0.42	✓2		✓2		✓2		
ddI EC (250mg)	HDPE bottle 30 capsules	$150	$12.50	$0.42					✓3		
ddI EC (400mg)	HDPE bottle 30 capsules	$240	$20.00	$0.67					✓3		
ddI (100mg)	HDPE bottle 60 tablets	$185	$7.69	$0.128					✓2		
ddI (200mg)	HDPE bottle 60 tablets	$181	$15.06	$0.251					✓2		
EFV (200mg)	HDPE bottle 90 capsules	$58	$14.50	$0.16					✓2		✓3
EFV (600mg)	HDPE bottle 30 tablets	$150	$12.50	$0.42	✓2	✓2	✓2		✓1,2		✓2
3TC (150mg) + d4T (30mg) + NVP (200mg)	HDPE bottle 60 tablets	$100	$8.30	$0.14	✓1,2	✓1	✓3	✓1	✓3		✓2
3TC (150mg) + d4T (30mg)	HDPE bottle 60 tablets	$62	$5.17	$0.09	✓1,2	✓3	✓2	✓1	✓3		✓1
3TC (150mg) + AZT (300mg) + NVP (200mg)	HDPE bottle 60 tablets	$159	$13.25	$0.22	✓2	✓1	✓3		✓2		
3TC (150mg) + AZT (300mg)	HDPE bottle 60 tablets	$119	$9.92	$0.17	✓1,2	✓1	✓2		✓1,2		✓1
3TC (150mg)	HDPE bottle 60 tablets	$36	$3.00	$0.05	✓1	✓1	✓1,2	✓1,2	✓1,2		✓1
LPV/r (200/50mg)	HDPE bottle 120 tablets	$550	$45.83	$0.38			✓3				
		$613	$51.08	$0.43	✓3				✓3		
NVP (200mg)	HDPE bottle 60 tablets	$45	$3.75	$0.06	✓1,2	✓1,2	✓3	✓1,2	✓1,2	✓2	✓1,2
d4T (30mg)	HDPE bottle 60 capsules	$36	$3.00	$0.05	✓3	✓2	✓1,2	✓1	✓1,2		✓1,2
TDF (300mg)	HDPE bottle 30 tablets	$135	$11.25	$0.38			✓2				
		$149	$12.42	$0.41	✓3						
TDF + 3TC (300/300mg)	HDPE bottle 30 tablets	$159	$13.25	$0.44			✓3				
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	$199	$16.58	$0.55			✓3				
TDF + 3TC + EFV (300/300/600mg)	HDPE bottle 30 tablets	$299	$24.92	$0.83			✓4				
TDF + FTC + EFV (300/200/600mg)	HDPE bottle 30 tablets	$349	$29.08	$0.97			✓4				
AZT (300mg)	HDPE bottle 60 tablets	$96	$8.00	$0.13	✓1	✓3	✓2		✓1,2		

PEDIATRIC PRODUCT		CEILING PRICE			SUPPLIER			
Name and strength	**Packaging**	**Per year**	**Per pack**	**Per pill/ml**	**Cipla**	**Matrix**	**Ranbaxy**	**Aurobindo**
ABC (20mg/ml)	HDPE bottle 240ml	$225	$14.99	$0.062				✓2
ABC 60mg	HDPE bottle 60 tablets	$82	$6.84	$0.114		✓3		✓3
ABC (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	$90	$7.50	$0.125		✓3		✓3
ddI EC (125mg)	HDPE bottle 30 tablets	$67	$5.59	$0.186				✓3
ddI EC (200mg)	HDPE bottle 30 tablets	$81	$6.71	$0.224				✓3
EFV (50mg)	HDPE bottle 30 tablets	$29	$2.43	$0.081				✓2
3TC (20mg) + d4T (5mg) + NVP (35mg)	HDPE bottle 60 tablets	$63	$2.70	$0.045			✓3	
3TC (40mg) + d4T (10mg) + NVP (70mg)	HDPE bottle 60 tablets		$5.25	$0.088			✓3	
3TC (30mg) + d4T (6mg) + NVP (50mg)	HDPE bottle 60 tablets	$54	$2.49	$0.042	✓2			
3TC (60mg) + d4T (12mg) + NVP (100mg)	HDPE bottle 60 tablets		$4.54	$0.076	✓2			
3TC (50mg/5ml)	HDPE bottle 240ml	$27	$1.77	$0.007				✓2
	HDPE bottle 100ml	$35	$0.98	$0.010	✓1,2			
3TC (30mg) + AZT (60mg)	HDPE bottle 60 tablets	$40	$3.30	$0.055		✓3		✓3
3TC (30mg) + AZT (60mg) + NVP (50mg)	HDPE bottle 60 tablets	$66	$5.50	$0.092		✓3		
LPV/r (100/25mg)	HDPE bottle 120 tablets	$389	$32.45	$0.270		✓3		✓3
NVP (50mg/5ml)	HDPE bottle 240ml	$58	$1.94	$0.008				✓1,2
	HDPE bottle 100ml	$71	$0.98	$0.010	✓3			
d4T (1mg/ml)	HDPE bottle 200ml	$48	$1.34	$0.007	✓2			✓2
d4T (15mg)	HDPE bottle 60 capsules	$9	$1.49	$0.025				✓2
d4T (20mg)	HDPE bottle 60 capsules	$11	$1.75	$0.03				✓2
AZT (50mg/5ml)	HDPE bottle 240ml	$64	$2.14	$0.01				✓2
	HDPE bottle 100ml	$72	$1.00	$0.01	✓1			
AZT (100mg)	HDPE bottle 100 capsules	$36	$5.00	$0.05	✓1,2			✓2

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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.

ARV Antiretroviral drug.

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 HIV/AIDS Initiative. Since 2002, the Clinton Foundation HIV/AIDS 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.

ddI 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.

EC enteric-coated.

EMEA 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 15th Updated List was published in March 2007 and includes 14 antiretrovirals and five fixed-dose combinations.

EFV or **EFZ** efavirenz; non-nucleoside analogue reverse transcriptase inhibitor.

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.

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.

FDC fixed-dose combination - multiple drugs combined in a single pill.

FPV fosamprenavir.

FTC emtricitabine; nucleoside analogue reverse transcriptase inhibitor.

Generic drug A pharmaceutical product usually intended to be interchangeable with the originator product, which is not protected by a patent in the country of production, or which is manufactured under compulsory or voluntary licence.

GPRM WHO Global Price Reporting Mechanism is 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, compile 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.

MTCT Mother-to-Child Transmission.

MVC maraviroc.

NDRA National Drug Regulatory Authority.

NGO Non-Governmental Organisation.

NFV nelfinavir; protease inhibitor.

NIH National Institutes of Health.

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor.

NRTI Nucleoside Analogue Reverse Transcriptase Inhibitor.

NtRTI Nucleotide Reverse Transcriptase Inhibitor.

NVP nevirapine; non-nucleoside analogue reverse transcriptase inhibitor.

OAPI Organisation Africaine de la Propriété Intellectuelle, African Intellectual Property Organisation, whose member states are Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Gabon, Guinea, Guinea-Bissau, Equatorial Guinea, Mali, Mauritania, Niger, Senegal, Togo.

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

PI Protease Inhibitor.

PLWHA People Living With HIV/AIDS.

PMTCT Prevention of Mother-to-Child Transmission.

ppy per patient per year.

R&D Research and Development.

RAL raltegravir.

RTV ritonavir; protease inhibitor.

r low-dose ritonavir, used as a booster.

SQV saquinavir; protease inhibitor.

TAC Treatment Action Campaign.

TB tuberculosis.

TDF tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

TPV tipranavir.

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.

U.S. FDA United States Food and Drug Administration.

VL voluntary licence.

WHO World Health Organization.

WTO World Trade Organization.

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

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