UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS

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12th EDITION

JANUARY 2010

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

New!

We're delighted to announce the launch of an online version of Untangling the Web of Antiretroviral Price Reductions, Médecins Sans Frontières' guide to the prices of AIDS medicines, now in its 12th edition.

The online version reproduces the features of Untangling the Web - an analysis of the access to antiretrovirals environment, individual drug profile pages with prices quoted by companies, charts representing the evolution in price in previous years, and a spotlight on access issues including a look at patents and paediatrics - in a clear, user-friendly and free-flowing design.

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Ten years ago, on the heels of Médecins Sans Frontières (MSF) being awarded the Nobel Peace Prize - and largely in response to the inequalities surrounding access to AIDS treatment between rich and poor countries – MSF launched the Campaign for Access to Essential Medicines. Its sole purpose has been to push for access to, and the development of life-saving and life-prolonging medicines diagnostics and vaccines for patients in MSF programmes and beyond. Untangling the Web of Antiretroviral Price Reductions, MSF's guide to the prices of AIDS medicines, is now in its 12th edition, and available for the first time as an online resource at utw.msfaccess.org.

Introduction

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

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

"It's a question of choice for governments. Will they give people in developing countries just a few extra years of life, or the same chance for long-term survival as people with HIV/AIDS in rich countries?"

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

MSF now provides treatment to 140,000 people in more than 30 countries and today a total of four million people across the developing world are on ART.[1] While this represents important progress, an approximately further six million people in immediate need of treatment are a testament to the persistent emergency.[2] With growing numbers of patients in developing countries having been on treatment for five years or longer, new challenges are emerging to ensure their long-term survival. In India alone nearly 240,000 people are accessing first-line ART under the national AIDS treatment programme.

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

However, about 60% of people in need of treatment today are not receiving it. The number of people in need of treatment will significantly increase with the recent revision of WHO guidelines which have recommended, in line with current evidence, that treatment be initiated earlier in a patient's disease progression. Starting treatment earlier will greatly reduce the risk of tuberculosis infections, among others.

Extending ARV treatment in developing countries to all people in need, while ensuring patients can survive with HIV in the long term, will require much more investment and political will. For treatment to be most successful, patients need to be monitored effectively and have access to newer and more potent drugs when they inevitably develop resistance or side effects to their medicines over time. But most newer drugs are unaffordable because they are protected by patents and crucial monitoring tests are not adapted for use in resource-poor settings.

Over the last decade, effective action by public interest groups and People Living with HIV/AIDS (PLHA) networks has raised the alarm and billions of dollars have been mobilised. However, the international AIDS effort is at a critical juncture, compromised further by the response of world leaders to the economic crisis: the two main funding sources for HIV/AIDS in developing countries, the Global Fund and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), will not be able to support the treatment scale-up at its current rate given insufficient donor commitment. The Global Fund is facing a significant financing gap and PEPFAR's funding levels are flat.

Given the unprecedented disease burden represented by HIV and the proportion of overall mortality caused by AIDS in most affected countries - including child and maternal deaths - HIV/AIDS continues to be a global emergency. An effective HIV/AIDS response, in particular access to treatment, has a positive population-level impact on adult, infant and under-five mortality.[3]

Only three years after world leaders met at the 2006 United Nations General Assembly and committed to universal access to HIV prevention, treatment and care, political and funding support is waning. The number of people who will need treatment by 2030 has been projected to reach as many as 55 million.[4] A sustained response to HIV/AIDS includes an obligation to put people on treatment and to continue treatment as medically required.

To ensure that funds stretch as far as possible to meet the needs, policy actions are needed to contain the cost of drugs, while ensuring quality treatment for the long term.

One of the most promising developments over the past year has been the green light given by the international drug purchase facility UNITAID to establish the licensing agency to run a patent pool for AIDS medicines. A patent pool could help overcome patent barriers and ensure swifter access to needed medicines at affordable prices, while boosting the development of new fixed-dose combinations and paediatric formulations. As it is a voluntary mechanism, the spotlight is now on the pharmaceutical industry and other patent owners to participate and make this groundbreaking mechanism the lifesaver it is intended to be.

Challenges: Second-Class AIDS Treatment

There is a growing disconnect between the AIDS treatment available to people in developed countries and to their counterparts in developing countries. In wealthy countries, AIDS now resembles a chronic disease, much like heart disease or diabetes, and patients generally have access to an increasing variety of treatment options once they inevitably develop drug resistance.[6]

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

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

- to a less toxic first-line regimen;
- to second- and third-line treatment options as patients develop resistance;
- better and timely detection of treatment failure through increased access to viral load testing; and
- to paediatric AIDS treatment options, which must be prioritised together with the prevention of mother-to-child transmission of the virus.

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

The Treatment Timebomb -- Report of the Enquiry of the UK All Party Parliamentary Group on AIDS[5]

Photo © Jonathan Torgovnik

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

The first line of defence to help slow the pace at which patients need to switch to newer, more expensive ARV treatment regimens is a robust first-line drug combination with few side effects. Today, the majority of people on their first-line of ARVs in low and middle-income countries receive the combination of lamivudine/stavudine/nevirapine (3TC/d4T/NVP).[7] Thanks to generic competition, this regimen now costs US$80 per patient per year (ppy) – 99% less than ten years ago. This dramatic price drop was possible because of competition among multiple generic manufacturers in countries where these drugs were not patented, such as Brazil, Thailand and India (see graph 1).

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

Stavudine is virtually no longer used in wealthy countries (in 2006, fewer than 2% of patients in Switzerland, for example were taking the drug).[8] Patients in these countries are offered better-tolerated alternatives, such as tenofovir (TDF) or zidovudine (AZT).

Until now, the significantly higher costs of these alternatives have largely prevented this switch in many developing countries. However, there has been noteworthy downward movement in the prices of less-toxic first-line combinations.

The price of tenofovir has come down significantly over the past year by over a third, to US$100 ppy for the lowest generic price. This means that TDF-based combinations are now nearly the same price as those containing zidovudine (see graph 2). Generic competition is steadily helping these prices to come down and prices can be expected to fall further with increased demand.

Design HIV drugs with developing country needs in mind

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

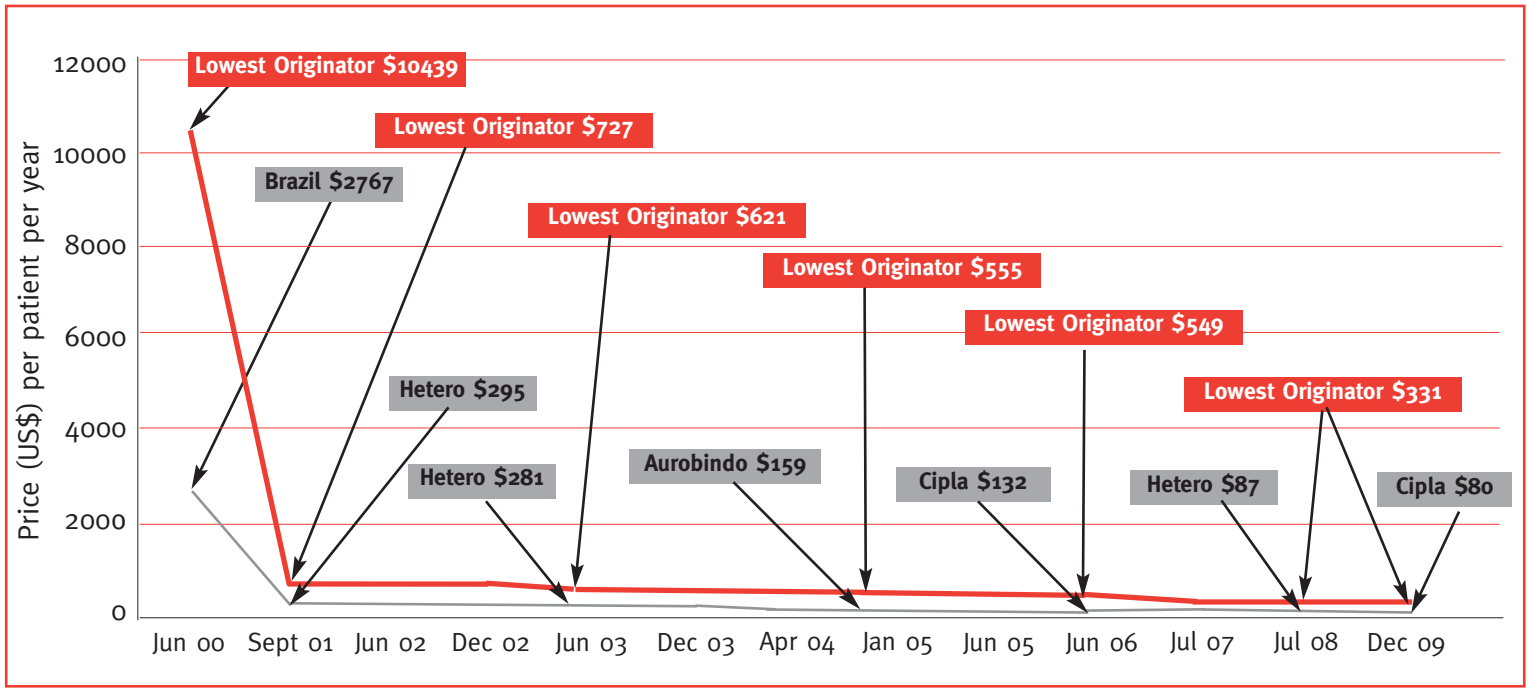
Over the last three years, there have been significant advances in HIV medicine, which have led to a number of new drugs from older classes, as well as entirely new therapeutic classes being approved for use. The new drug classes have different mechanisms of action to target the HIV virus, providing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

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

Further, there is currently no safety and efficacy data for children for the new drugs etravirine, maraviroc, or raltegravir and still no data for tenofovir. For other drugs there are limited data: for efavirenz (no data for children under three years), atazanavir and darunavir (no data for children under six years). This despite the fact that the U.S. Food and Drug Administration (FDA) has included incentives and obligations to encourage submission of data for paediatric use since 1997[14] and the European Medicines Agency (EMEA) followed suit in January 2007.[15]

The need for high-tech monitoring can also affect the availability of antiretrovirals. For instance, the entry inhibitor maraviroc requires the HIV virus to have the chemokine co-receptor 5 (CCR5) 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 impracticable and unaffordable in developing country contexts where even simple laboratory monitoring is rarely available.

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

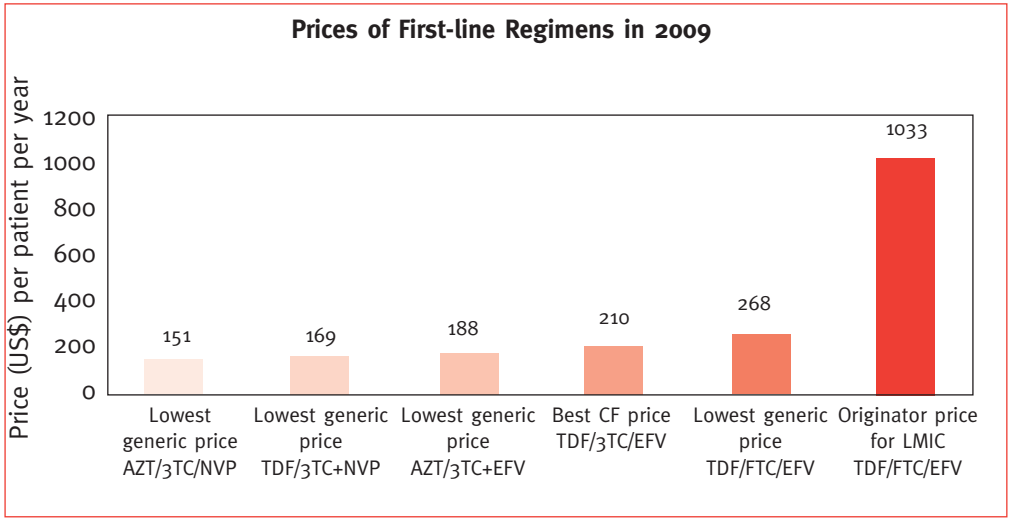


In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and in its place, develop a plan to move towards zidovudine- or tenofovir-based first-line regimens.[375]

The impact of such a move on treatment programme budgets is evident. At best the price of first-line regimens almost doubles. For TDF-based regimen in some middle-income countries unable to access generic products due to patent protection, the price increases almost thirteen fold. In their one-pill-once-a-day version, generic triple FDCs containing tenofovir are now available for US$210 ppy, down 51% over the past two years. Notably, the originator company price for the FDC containing tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) has not changed in the past two years and remains far higher at US$ 613 ppy for low-income countries. And in some 'middle-income' countries, where generics are not available due to patents, the originator price for the FDC remains exorbitant, at US$ 1,033 ppy.

Although better, less-toxic first-line regimens are still at best nearly double the price of the most-commonly used first-line regimen, the long-term benefits of patients being able to tolerate and stay on their first ARV combination longer can outweigh the costs. A study in South Africa

Graph 2: *The impact of changing regimens on the price of first-line ARV treatment.*



showed that the increased cost of providing the lowest-priced generic tenofovir-based regimen would be offset with savings on the cost of managing the side effects of stavudine.[10] And while shifting treatment programmes to a new first-line regimen brings with it clear logistical challenges on top of cost concerns, it is critical that treatment providers begin moving away from stavudine as has been done for example in Zambia, Lesotho, Guyana, and Botswana.

B) Secure access to second- and third-line regimens

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

Demand for newer AIDS drugs is growing fast. In one of MSF's longest-running AIDS treatment programmes, in Khayelitsha, South Africa, 16% of patients on treatment for five years needed to switch to a second-line drug combination because of resistance. And 25% of those patients who switched again developed virological failure to their second-line regimen a further two years later.[11]

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

Mpumi Mantangana, MSF nurse in Khayelitsha, South Africa

MSF's Khayelitsha data provides a window into the growing need for access to newer AIDS drug regimens and improved laboratory tools across the developing world in the coming years. However, the cost of newer regimens and laboratory tools remains a major barrier to access.

New WHO guidelines on second-line further simplify and prioritise the choice of regimens. Second-line regimens may, in the future, be as low as US$ 425 ppy (see graph 3). This is 2.8 times more than the cheapest WHO-recommended first-line regimen.

As some patients in developing countries have already developed resistance to their second-line regimen, it is crucial to secure further treatment options essential to long-term survival. The price of a potential third-line ARV regimen, however, could cost at least 15 times the WHO-recommended first-line regimen because of patent barriers, and at least 5.4 times what the cheapest second-line regimen costs.

The new recommendations for the first time call for the need for third-line therapy. As many studies are ongoing, drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.[375]

Death at the doorstep: Thembisa's story

Photo © Global Health TV

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

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

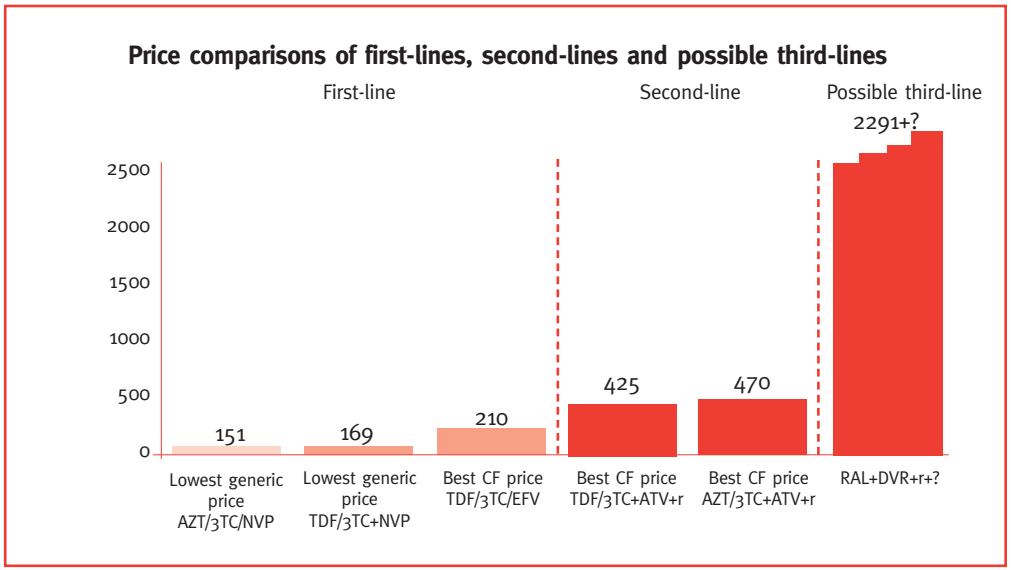
Thembisa is but one of many patients who now need access to newer and more potent, but unaffordable ARV regimens.

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

For the first time a price for raltegravir has been announced for low-income countries at US$ 1,113 ppy. No pricing for developing countries has been announced for etravirine. As raltegravir and boosted darunavir would be only two of three components, it is estimated that a third-line regimen could exceed US$ 2,291 ppy. For most people who are failing on their second-line combination already, this unaffordable price will mean they almost certainly once again face death.

There is no room for complacency about these prices. Unlike with the first generation of AIDS drugs, patents in key producing countries such as India prevent the production of much more affordable generic versions: many of the newer ARVs will be patentable in India, and several such as raltegravir, maraviroc or etravirine already are. The lack of competition among generic manufacturers means that prices cannot be expected to come down the way they did for the first generation of ARVs.

It is imperative that governments undertake measures to ensure that people in need of newer and more potent ARVs are not denied access because of patent barriers. The UNITAID patent pool for antiretrovirals is an important additional mechanism to ensure future availability of affordable essential medicines.



Graph 3: *The treatment timebomb: the impact of switching to second- and third-line regimens on the price of ARV treatment. Changing a patient's regimen because of side effects or the emergence of resistance from first-line regimens to second-line regimens recommended by WHO involves a considerable price hike. For third-line regimens, many of the newer antiretrovirals will be patentable in India, and several such as raltegravir already are. Treatment providers are once again faced with the prospect of drugs being priced out of reach.*

C) Put an end to the neglect of children living with HIV/AIDS

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

The vast majority of children with HIV/AIDS are infected through transmission from the mother during

Photo © Brendan Bannon

pregnancy, childbirth or breastfeeding. PMTCT has been so successful in wealthy countries that nearly no children are newly infected with AIDS. But in developing countries, nearly 370,000 new child infections occurred in 2007 - a testament to the failure to effectively implement simplified and efficient PMTCT strategies that could dramatically reduce the number of child infections. Such strategies include the provision of triple ART to all HIV-positive pregnant women and introducing ways to protect the child throughout the breastfeeding period.[17] This would lessen the need for paediatric treatment, as has been the case in wealthy countries.

Because there are so few children with HIV/AIDS in wealthy countries, there is very limited investment by the pharmaceutical industry into

developing appropriate and adapted paediatric ARVs. There are several available paediatric fixed-dose combination tablets that come in doses for various child sizes and the price of the paediatric FDC d4T/3TC/NVP is finally lower than that for adults, at US$61 ppy. But the fact that the first WHO prequalified paediatric ARV FDC became available only in 2006, while the adult equivalent has been available since 2001, reflects the way in which children with AIDS lag behind.

Furthermore, of the 22 ARVs approved by the U.S. FDA for adults, six are not approved for use in children and seven do not have any paediatric formulations.[18] 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 LPV/r for infants that have been exposed to nevirapine directly or 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. At the same time, there is no alternative regimen once the child fails this regimen. There is thus an urgent need for the development of child-friendly doses of heat-stable protease inhibitors for the youngest patients and urgent dosing studies for the newer more potent drugs need to be conducted.

Overcoming Challenges: Staving off the Second Wave of the Access Crisis

Unaffordable, again...

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

Develop simple diagnostic and monitoring tools for adults and children

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

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

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

Furthermore, HIV/AIDS diagnosis in infants is extremely difficult. In babies under 18 months it can only be conducted with the use of a complex DNA-based diagnostic test that is expensive to conduct, also requiring trained personnel and access to sophisticated laboratory equipment. Only 15% of children born to mothers living with HIV in low and middle income countries were tested for HIV within the first two months of life.[16] There is a desperate need to develop a simple diagnostic test that can be used to detect the virus in younger infants on the spot, so that treatment can be initiated as early as necessary. Early infant diagnosis is key because without treatment, half the children will die before the age of two.

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

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

Across the globe, increased product patenting in developing countries is now systematically ensuring that more affordable generic versions of medicines cannot be produced. Under the World Trade Organization's TRIPS Agreement (Trade-Related Aspects of Intellectual Property Rights) and the 2001 Doha Declaration on TRIPS and Public Health, least-developed countries (LDCs) are not required to grant or enforce patents on pharmaceuticals until 2016. But international trade rules now require the patenting of medicines in key producing countries like India and Brazil, essentially eliminating the kind of generic competition for the future that brought prices down in the past.

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 TRIPS Agreement, such as compulsory licensing. There is an additional way - the participation of pharmaceutical companies - originator and generic - in new mechanisms to boost access. Ensuring newer medicines are made affordable for people in developing countries thus depends on:

- a country's right to design pro-access patent laws;
- a country's right, when essential medicines are patented and unaffordable, to issue compulsory licenses to ensure access;
- pharmaceutical companies participating in the new HIV medicines patent pool, the innovative mechanism being established by UNITAID.

A) Design flexible patent laws

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

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

India's pro-access patent law

Not all patent applications are valid.

Many of the applications do not claim real 'inventions' and therefore should not deserve a patent. Many patent applications are for a new use of an old drug, or simply for derivatives of old drugs or combinations of old drugs. The Indian Patents Act, if rigorously interpreted, provides under Section 3(d) several grounds for rejecting a patent application, for instance if the patent claimed is only a new form of a known pharmaceutical substance.

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

Novartis launched a legal proceedings challenging public health safeguards in India's patent law in an attempt to strike down Section 3(d) of India's Patents Act. This prompted MSF to launch the 'Drop the Case' petition in order to protect the 'pharmacy of the developing world'.[20] Novartis lost this case in August 2007 when the Madras High Court upheld the public health safeguard.

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

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

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

The Treatment Timebomb -- Report of the Enquiry of the UK All Party Parliamentary Group on AIDS[19]

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

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

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

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

Three down; many more to go: Opposing patents in India in the name of access to affordable medicines

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

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

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

B) Keep the door open for competition, despite patents

When drugs are patented, and pharmaceutical companies fail to fulfill their obligation to make patented medicines available and affordable to patients in developing countries, the only way to bring prices down is either through compulsory licensing or voluntary licensing which allows generic production. In both cases, royalties are paid to the patent holder.

Compulsory Licensing

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

The case of the CL issued by Thailand for 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 ppy to under US$900 in Thailand and US$550 in countries in the Clinton Foundation Consortium. Similarly, a CL issued by Brazil for efavirenz in May 2007 brought the cost for the drug in Brazil down by almost 70%.

Even though issuing a CL is entirely in line with WTO rules, countries that take the step typically face immense direct and indirect retaliatory measures and pressure from developed country governments and the pharmaceutical industry. This can serve to discourage

Photo © Zethu Mlobeli/MSF

other countries that are considering issuing CLs. In a world in which medicines are becoming increasingly patented, CLs, including those for export, will be a critical mechanism to help ensure that essential medicines are affordable enough for people to access them and countries must feel supported in their right to increase access to needed medicines for their citizens.

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 merely to extend the originator company's control over a given market, stipulating conditions such as which source the active ingredient must be purchased from, as well as to which countries the drugs can be exported. Such restrictive VLs ultimately do not lead to the unhindered competition that allows patients to benefit from the lowest prices possible.

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

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

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

C) Pool patents and take the plunge for affordable treatment

Company-led 'access' schemes have proven to be minimally effective. 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 Colombia, are often left out of the discount scheme altogether or are offered only minimal discounts. Primarily the threat of losing a patent or having a patent barrier removed is what makes companies respond and reduce prices.

Stop the deliberate confusion of quality generic medicines and counterfeit medicines

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

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

The dangers of overbroad IP protection are illustrated by the recent use of European Union customs rules, which are used to help enforce EU patents and trademarks. These rules have in fact prevented the timely access to life-saving medicines. Several shipments of generic medicines - including AIDS drugs - have been detained in transit through European countries based on allegations of IP infringement, even though they are not protected by IP rights in the countries of export or import. This has affected the supply of essential medicines from manufacturers in India to patients in developing countries in Africa and Latin America. The EU customs rules should be amended to prevent this occurring again.

Another example is the Kenyan Anti-Counterfeiting Act which passed in December 2008, and which uses a definition of counterfeiting so wide that it includes all products that are copies of patented goods. This would also cover quality-assured and legally-produced generic medicines. The Act thus has the potential to seriously endanger access to generic medicines, such as those used by MSF and other treatment providers in Kenya. It is critical that the Act be revised. Public health groups are seeking a judicial review on the grounds that the new legislation contravenes their 'right to life' under the Kenyan Constitution.

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

One major problem that is not addressed by the use of the excessively general term 'counterfeit', and which MSF teams face in many countries, is posed by substandard drugs. These are drugs from originator companies as well as from generic producers that do not meet international standards for quality. To address the problem of sub-standard medicines, measures should be undertaken including by WHO to assist manufacturers in improving their production processes to ensure quality standards are met, and to provide long-term technical assistance to strengthen national drug regulatory authorities.

To date, though, the focus of the response to these questions has been placed on protecting commercial interests, rather than addressing serious public health issues. This has meant diverting attention from what needs to be done. It is important that the WHO and other key public health actors refocus the debate on the public health issues in relation to the availability, safety efficacy and quality of medicines, and that proposals for greater protection of commercial interests that threaten access to medicines are rejected.

There is one way companies could act to make a difference, however. The international drug purchase facility UNITAID has just created a 'patent pool' for AIDS medicines. If successful, this mechanism will make it possible to access needed medicines much more quickly and at much more affordable prices than today and lead to the development of much-needed medicines adapted to patients' needs.

Instead of having patents act as barriers, companies, researchers or universities license the patents on their inventions to one entity: the patent pool.

In this way, any company that wants to use the inventions can get a licence from the pool, under pre-determined licensing terms, in exchange for royalties. It could then produce generic versions of the patented inventions and export them to countries covered by the licence. The licences should be valid for a wide geographical area, which would mean a sufficiently attractive, large market for potential producers. This process will encourage multiple producers to come forward, resulting in competition between producers and bringing drug prices down.
The patent pool would help increase access to ARVs in three key areas:

1. It would help foster competition among multiple manufacturers, bringing prices down for newer and more potent medicines needed by increasing numbers of patients;

2. It would help facilitate the creation of new and needed fixed-dose combinations, where otherwise patents on the individual drug compounds stand in the way; and

3. It would help support the development of paediatric ARV formulations and combinations, by eliminating patent barriers.

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

Médecins Sans Frontières is calling for all patents on the following antiretrovirals (and combinations thereof) to be put in the UNITAID patent pool:

lopinavir, ritonavir (Abbott Laboratories);

nevirapine, tipranavir (Boehringer Ingelheim);

didanosine, atazanavir (Bristol-Myers Squibb);

lamivudine, abacavir, fosamprenavir, S/GSK1349572 (GlaxoSmithKline);

tenofovir disoproxil fumarate, emtricitabine, GS-9350, elvitegravir (Gilead Sciences);

efavirenz, raltegravir (Merck);

maraviroc (Pfizer);

SPI-452 (Sequoia Pharmaceuticals);

darunavir, etravirine, rilpivirine (Johnson & Johnson/Tibotec Pharmaceuticals)

In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.

Conclusion

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

At the same time, steps must be undertaken to ensure that people in developing countries are receiving the optimal monitoring and treatment that supports their long-term survival, comparable to their counterparts living with HIV/AIDS in wealthy countries. This means securing access to needed monitoring tools, while providing patients both with a robust first-line regimen that has few side effects, as well as ensuring there are treatment options for when patients show signs of virological failure and need to switch to a second- or third-line combination. Although prices for certain key newer medicines have come down significantly because of competition among generic manufacturers and increased demand, overall prices for newer drugs remain unaffordable for developing countries and out of reach of national treatment programmes.

Countries must be supported in their use of flexibilities in international trade rules to help bring prices of newer drugs down more systematically and speedily, so that the growing number of people in need of newer and more potent drugs has immediate access once they require them. Pharmaceutical companies must be urged to participate in the patent pool created by UNITAID, so that needed formulations can be made available to developing countries more swiftly and at much more affordable prices.

And it is critical that HIV/AIDS continues to be treated as the emergency it is. Funding levels must be increased to take on the massive task of providing sustained AIDS treatment in developing countries. The worrying trend of treatment providers needing to scale back ART at a time when they should be scaling up must be countered with sustained and reaffirmed commitment by leaders and donors to universal access to HIV/AIDS treatment.

Quality Issues

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

Readers and purchasers wishing to obtain more information about drug quality are therefore encouraged to consult the WHO list of Prequalified Medicinal Products which contains the products that "meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis medicines."

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

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

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

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

Quality of drugs in the data provided in Untangling the Web

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

But not all the products listed in this report have been prequalified by WHO and only some of them are used by MSF in its own projects. Products included in the WHO List of Prequalified Medicinal Products (as of December 2009), including the ones approved by Health Canada, EMEA through article 58, U.S. FDA or tentatively approved by U.S. FDA, appear in bold in the tables of drug prices. Please consult the WHO website (http://mednet3.who.int/prequal/) for the latest list of prequalified products and for information on the status of dossier assessment.

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 December 2009.

All originator companies marketing ARVs were included in the survey. But the list of generic producers is by no means exhaustive. Only generic companies that have at least one ARV listed on the WHO 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 May 2009.

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, Hetero has 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."

- 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).
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 glossary.
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

- 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 drug profiles. 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 eight 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. This is an example of pooled procurement and how it can have an impact on price reductions.

- 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://apps.who.int/prequal/

How to Read the Drug Profiles

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

Table 1: 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 WHO List of Prequalified Medicinal Products is a list of manufacturers and suppliers who meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis medicines. Products included in the WHO List of Prequalified Medicinal Products for Antiretrovirals (as of December 2009) are in **BOLD** in the tables of drug prices.

Readers and purchasers wishing to obtain more information about the quality of ARVs are encouraged to consult the WHO Prequalification Program website as this list is updated regularly (http://apps.who.int/prequal/).

The Clinton Foundation's HIV/AIDS Initiative negotiates with several manufacturers for reduced prices for 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.

Chart 1: 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 the purpose of 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 considered 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)

General information

- Therapeutic class: chemokine co-receptor 5 (CCR5) antagonist (entry inhibitor).
- Not currently included in WHO guidelines.
- Indicated for treatment-experienced adult patients infected with only CCR5 tropic HIV-1 detectable strains, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.[185]
- Originator company and product name: Pfizer, Selzentry. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approved by the U.S. Food and Drug Administration (FDA): 7 August 2007.[186]
- Not included in the WHO Model List of Essential Medicines (EML).[187]
- Basic patent was applied for by Pfizer in December 1999[188] and is due to expire in 2019. In May 2001, Pfizer applied for an additional patent more specifically related to crystalline maraviroc.[189]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

Maraviroc (MVC) is classed as a CCR5 co-receptor antagonist that targets the penetration of cells by the HIV virus. This drug option is predominately used in the developed world as "salvage therapy" for patients who are already resistant to multiple drug classes. Not all patients will benefit from this drug, as only some HIV viruses use this CCR5 co-receptor. The recommendation is for patients to have a tropism test to look for this co-receptor prior to treatment. Today, this test is not widely available and is expensive, at approximately US$ 1,900.[193] 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 communicated it does not offer a reduced price for developing countries.

Patents Pfizer obtained a patent in India in October 2007.[190]

This patent blocks the manufacture of generic formulations of MVC in India, limiting the much-needed competition that historically has been shown to lead to price reductions. Pfizer has applied for product patents and patents for the crystal form in Brazil, South Africa, India, China and ARIPO[191] and OAPI countries.[192] To date, patents on the crystal form have been granted in India, China, and ARIPO and OAPI countries.

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

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.[114]
- Originator company and product name: Roche and Trimeris, Fuzeon.
- First approved by the U.S. Food and Drug Administration (FDA) in March 2003.[115]
- Not included in the WHO Model List of Essential Medicines (EML).[116]
- Basic patent on enfuvirtide applied for by Duke University in June 1994,[117] 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,[118] 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.[119] In November 2007, Novartis Vaccines and Diagnostics filed a suit against Roche and Trimeris, alleging infringement of Novartis's patent.[120]

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 developed in the fusion inhibitor class. 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. 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 per year is prohibitive for many developing countries that may have a need for this product.[121]

In Brazil, enfuvirtide is available at US$ 16,717 per patient per year.

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

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

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.[215]
- Originator company and product name: Merck & Co., Isentress.
- First approved by the U.S. Food and Drug Administration (FDA): 12 October 2007.
- Not included in the WHO Model List of Essential Medicines (EML).
- World sales of originator product in 2008: US$ 361.1 million;[216] 2007: US$ 41.3 million.
- The basic patent was applied for in October 2002 by the Institute for Research in Molecular Biology (IRBM), Pomezia, Italy, one of Merck's research sites.[217] The patent is due to expire in 2022. In 2005, Merck and IRBM applied for another patent on the potassium salt of RAL.[218]

Price information:

Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Merck	
		Category 1	Category 2
Eligibility restrictions		see annexes 2 and 10	
RAL 400mg tablet	2	1113 (1.525)	not available

Spotlight on access issues:

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

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

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

This is the first edition that includes tiered pricing by Merck for raltegravir (see annex 10). The price is nevertheless extremely high and therefore unaffordable for developing countries, and there is no generic version available.

RAL pricing for category 2 countries (see annex 10) is still unknown.

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[219] which will expire in 2024. Generic competition to reduce the price of the medicine will therefore only be possible through voluntary licences issued by the patent holder, or through compulsory licences issued by the government.

Merck has also filed patent applications for the potassium salt form of RAL which, if granted, will further extend Merck's monopoly to 2027.

Paediatrics The safety and efficacy of RAL in patients under 16 years 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).[80]
- 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.[81]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[82]
- World sales of originator product: 2008: US$ 1.149 billion; 2007: US$ 956 million; 2006: US$ 791 million; 2005: US$ 680 million; 2004: US$ 621 million; and 2003: US$ 544 million.[83,84,85,86]
- The basic patent on EFV was filed in 1993 by Merck, and is due to expire in 2013.[87]

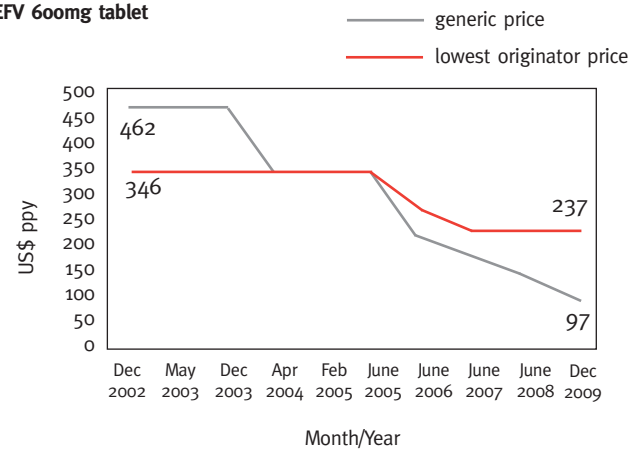
Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Merck		Aurobindo (CF)	Cipla (CF)	Emcure	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
		Category 1	Category 2						
Eligibility restrictions		see annexes 2 and 10		None	None	None	None	None	None
EFV 50mg capsule	--	**(0.120)**	**(0.210)**	**(0.087)**					
EFV 50mg tablet	--	**(0.120)**	**(0.210)**						
EFV 100mg capsule	--			**(0.150)**					
EFV 200mg capsule	3	**394 (0.360)**	**821 (0.750)**	**152 (0.139)**	**146 (0.133)**			**171 (0.156)**	
EFV 200mg tablet	3	**394 (0.360)**	**821 (0.750)**						**128 (0.117)**
EFV 600mg tablet	1	**237 (0.650)**	**657 (1.800)**	**97 (0.267)**	**107 (0.292)**	**97 (0.267)**	**107 (0.292)**	**145 (0.397)**	**103 (0.281)**
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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.

EFV 600mg tablet



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

As of December 2009, there were seven generic sources of EFV 600mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Since 2002, the originator price has decreased by 32%, while generic prices have dropped by 79%.

Spotlight on access issues:

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

In its new 2009 guidelines, WHO recommends the use of EFV - in combination with two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF) - as a preferred first-line ART.[375]

EFV is also recommended as the preferred NNRTI for patients starting ART while on tuberculosis treatment. Rifampicin, one of the main drugs used to treat TB, interacts with nevirapine (NVP), resulting in lower blood levels of NVP. EFV, however, does not have the same degree of interaction, and can be used as an alternative.
Its price, however, remains high, particularly for countries included in Merck's second pricing tier (see annex 10), where the cost of EFV alone can exceed eight times the cost of the most widely-used triple FDC (3TC/d4T/NVP).

Merck plans to phase out the 200mg and 50mg capsule formulations, which will be replaced by tablets.

Patents Despite generic competition from a number of Indian manufacturers, EFV remains expensive in countries where Merck holds patents that block the production and sale of generics.

In countries where EFV is patented, governments and civil society groups have taken various measures to ensure generic competition and lower prices, including:
• In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government is now purchasing EFV at US$ 106 per patient per year (ppy), which is 80% lower than the previous price of US$ 511 ppy.[88,89]
• In May 2007, Brazil, after numerous unsuccessful negotiations with Merck, issued a compulsory licence to import more affordable generic versions of EFV from India. At the time, the price of EFV in Brazil was US$ 580 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a generic version prequalified by WHO for US$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched the national generic version for use in the Brazilian health system.[90]
• In South Africa, Merck's refusal to allow sufficient generic competition contributed significantly to the high price of the drug. This led the AIDS Law Project (ALP), acting on behalf of the Treatment Action Campaign (TAC), to file a complaint before the Competition Commission in November 2007. As a result, Merck recently agreed to license its product to other producers, opening the opportunity for generic competition in South Africa, which is expected to drive down the price of EFV in the country.[91]
• In India, a patent for the process of preparing form 1 of crystalline EFV was granted in June 2005.[92] Even though Merck does not hold a product patent for EFV, this recently granted process patent appears to protect a key process for manufacturing EFV, and could therefore have an impact on generic production of EFV in India. This patent has therefore been opposed by Indian civil society organisations using the post-grant opposition procedures enshrined in India's patent law.[93]

In addition, Gilead[94] and BMS have filed patent applications related to combinations of EFV with other ARVs. In particular, BMS's efforts to receive a patent for the once-a-day pill EFV/FTC/TDF[95] will have an impact on access to improved first-line ARV treatment in the developing world. In India, the patent office has already rejected Gilead's application,[96] as combinations of known molecules are not patentable under India's patent law.

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

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

ETRAVIRINE

General information

- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Not currently indicated in WHO guidelines.
- Approved by U.S. Food and Drug Administration (FDA) for treatment-experienced adult patients who have evidence of resistance to an NNRTI and other antiretroviral agents.[122]
- Originator company and product name: Tibotec Pharmaceuticals, Intelence.
- First approved by the U.S. FDA: 18 January 2008.[123]
- 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.[124] Both Janssen Pharmaceutica and Tibotec are now part of Johnson&Johnson.[125,126]

Price information:

Prices in US$ quoted by companies for eligible developing countries

No reduced pricing available for developing countries.

Spotlight on access issues:

In December 2009, WHO released new recommendations which for the first time call for the need for third-line therapy. As many studies are ongoing, the drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.[375]

Etravirine was approved by the U.S. FDA in January 2008, and received marketing approval by the EMEA in August 2008. It has not yet been approved by any developing country health authority.

Tibotec was asked to provide a price for this product for inclusion in this publication, and the company communicated that etravirine will be included in its "Global Access Program."

However, for the second year in a row, 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 molecule patent in India.[127]

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

It is important to note that Tibotec has applied for the subsequent patents, even though Janssen Pharmaceutica is the holder for the molecule patent. To prolong the patent monopoly it is expected that a number of applications relating to etravirine will be for new forms and combinations.

Paediatrics Etravirine is not approved for use in children today. A waiver of paediatric studies from birth to two months was granted by EMEA on grounds that the medicine does not represent significant therapeutic benefit over existing treatments.[128]

NEVIRAPINE (NVP)

General information

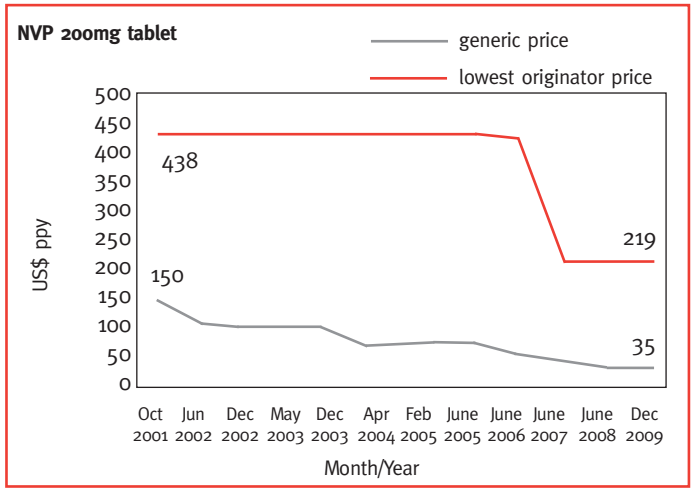
- Therapeutic class: non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Indicated for first- and second-line for adults, adolescents and children (WHO 2006 guidelines).[202,203]
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune.
- First approval by U.S. Food and Drug Administration (FDA): 21 June 1996.[204]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[205]
- World sales of originator product: 2007: US$ 412 million; 2006: US$ 370 million; 2005: US$ 386 million; 2004: US$ 378 million.[206,207,208,209]
- The basic patents on NVP were applied for by BI in November 1990, and are due to expire in November 2010.[210] BI also applied for a patent on the hemihydrate form of NVP, used in the suspension in 1998, which is due to expire 2018.[211] Additionally, BI applied for a patent on the extended-release formulation of nevirapine in 2008, which is due to expire in 2028.[212]

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

	Daily dose	Boehringer Ingelheim		Aurobindo (CF)	Cipla (CF)	Emcure	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)**	**42 (0.058)**	**35 (0.048)**	**42 (0.058)**	**35 (0.048)**	**42 (0.058)**	**47 (0.065)**	**42 (0.057)**
NVP 10mg/ml suspension	20ml	**380 (0.052/ml)**	**533 (0.073/ml)**	**66 (0.009/ml)**	**73 (0.010/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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were ten generic sources of NVP 200mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List 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 approximately 16% of the originator price.

NEVIRAPINE (NVP)

Spotlight on access issues:

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

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

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

However, after India introduced patent protection for pharmaceutical products in 2005, BI applied for a patent on the hemihydrate form of NVP, which relates to the paediatric suspension. Civil society groups in India filed a pre-grant opposition to BI's patent application in May 2006. In June 2008, the patent application on the NVP hemihydrate was rejected by the Indian patent office, allowing for unrestricted competition on the paediatric formulation. This constitutes an important victory for Indian civil society, as this is the first patent application related to a HIV medicine to have been rejected as a result of a pre-grant opposition.[213]

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

To give clinicians flexibility in prescribing ARV regimens, there is a need for a simple adapted formulation of NVP. The Paediatric Aids Working Group at WHO has given "urgent" priority to the development of a 50mg tablet.

In addition, with the increased prevalence of TB/HIV co-infection, there is a need for further studies into the interactions between NVP and the TB drugs, rifampicin and rifabutin in children.[214]

BI has a NVP donation programme 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. It therefore costs more to treat a 10kg child with NVP, than an adult.

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

ABACAVIR (ABC)

General information

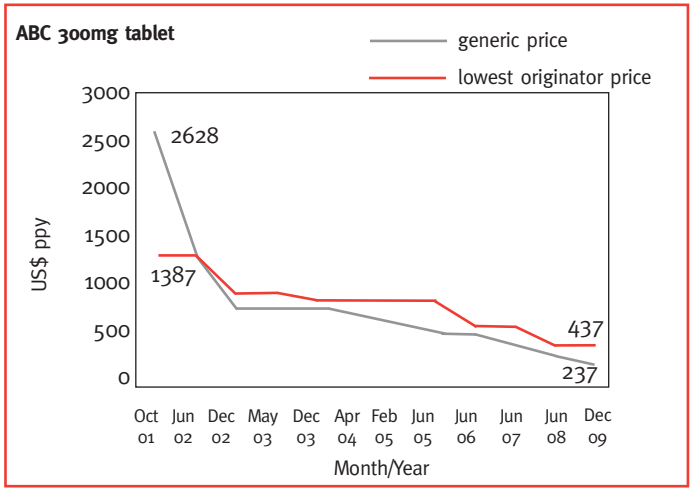
- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults, adolescents and children (WHO 2006 guidelines).[21,22]
- Originator company, and product brand name: GlaxoSmithKline (GSK), Ziagen. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): 17 December 1998.[23]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[24]
- World sales of originator product for 2008: US$ 175 million; 2007: US$ 215 million; 2006: US$ 230 million; 2005: US$ 268 million; 2004: US$ 290 million.[25,26,27,28,29]
- The basic patents on ABC were applied for by GSK in 1989[30] and 1990,[31] 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[32] and on compositions of ABC particularly relevant for paediatric use in 1999,[33] 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)	Matrix (CF)	Ranbaxy	Strides
Eligibility restrictions		see annex 2	None	None	None	None	None
ABC 300mg tablet	2	**437 (0.599)**	**261 (0.358)**	**237 (0.325)**	**243 (0.333)**	**341 (0.467)**	
ABC 20mg/ml oral solution	10ml	**230 (0.063)**	**230 (0.063/ml)**	**204(0.056/ml)**			
ABC 60mg tablet	4		**183 (0.125)**	134 (0.092)	**183 (0.125)**		730 (0.500)

(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.

Products included in the WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were four generic sources of ABC 300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Since 2001, the originator price has decreased by 68%, while the generic price has decreased by 91%.

ABACAVIR (ABC)

Spotlight on access issues:

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. Recommendations for second-line treatment include PIs such as ritonavir-boosted atazanavir (ATV) or LPV/r, and simplified NRTI options. Abacavir (ABC) and didonasine (ddI) are no longer recommended as the backbones of NRTI in second-line therapy.[37][5]

Even though the price of ABC has fallen by almost 91% in generic pricing since 2001, the current lowest generic price is more than two times the lowest price of tenofovir (TDF) or zidovudine (AZT). Additionally, GSK's differential pricing structure (see annex 2) excludes non-African countries that are not funded by the Global Fund. This structure leaves these countries paying more than US$ 4,300 per patient per year.[38]

Patents As shown in the graph, 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.[34] However, the patent more specifically related to paediatric formulations was granted in December 2007.[35] 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.

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

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

Today, once-daily dosing of ABC is only recommended for patients over 12 years of age; more studies are needed to confirm the safety of daily dosing of ABC in children.[36]

DIDANOSINE (ddI)

General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for second-line for adults, adolescents and children.[75]
- 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.[76]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[77]
- 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.[78]
- The 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.

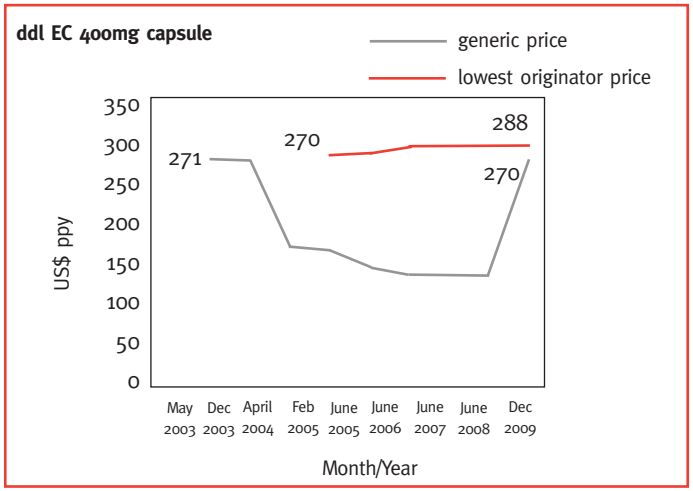
Price information: Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Bristol-Myers Squibb		Aurobindo (CF)	Cipla	Ranbaxy
		Category 1	Category 2			
Eligibility restrictions		see annexes 2 and 7		None	None	None
ddI 25mg tablet	5	**212 (0.116)**	**433 (0.237)**		115 (0.063)	228 (0.125)
ddI 50mg tablet	--	**(0.158)**	**(0.237)**		(0.079)	(0.115)
ddI 100mg tablet	4	**310 (0.212)**	**366 (0.251)**	**207 (0.142)**	188 (0.129)	242 (0.166)
ddI 150mg tablet	--	**(0.308)**	**(0.348)**	**(0.225)**	(0.167)	
ddI 200mg tablet	--			**(0.283)**	(0.257)	
ddI 125mg enteric-coated capsule	--			**(0.186)**		
ddI 200mg enteric-coated capsule	--			**(0.224)**		
ddI 250mg enteric-coated capsule	1	**223 (0.611)**	**249 (0.683)**	**172 (0.471)**	103 (0.283)	
ddI 400mg enteric-coated capsule	1	**288 (0.789)**	**322 (0.881)**	**270 (0.740)**	132 (0.363)	
ddI 2g powder for reconstitution (Final concentration 10mg/ml)	12ml	**276 (12.590/2g)**	**308 (14.057/2g)**	**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.

Products included in the WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold**.

DIDANOSINE (ddI)



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

As of December 2009, there was one generic source of ddI 400mg EC listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Spotlight on access issues:

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted ATV or LPV/r, and simplified NRTI options are recommended. Abacavir (ABC) and didanosine (ddI) are no longer recommended as one of the NRTI backbones in second-line therapy.[375]

BMS's differential pricing structure limits the prices quoted above to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries paying more than US$ 3,200 per patient per year for ddI enteric-coated (EC) 400mg capsules, which is prohibitive for many of these countries.[369]

In 2006, BMS discontinued the sale of the chewable / dispersible buffered tablets in the U.S. The enteric-coated capsules are more adaptable as they can be taken once daily and, unlike the tablets, do not contain a buffer. The buffer has been associated with stomach upsets and a bitter and chalky taste.

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

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

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

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

BMS offers no differential price for the ddI EC 125mg, which is the best-adapted option for older children who can swallow. The price in the developed world, at more than US$ 1,000 per patient year, is prohibitive for the developing world.

EMTRICITABINE (FTC)

General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults.[97]
- First approval by U.S. Food and Drug Administration (FDA): July 2003.[98]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[99]
- World sales of originator product: 2008: US$ 31.1 million; 2007: US$ 31.5 million; 2006: US$ 36.3 million; 2005: US$ 47.4 million; 2004: US$ 57.6 million.[100,101,102]
- The basic patent on FTC and lamivudine (3TC) was filed by IAF Biochem in 1990 and is due to expire in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.[103,104]
- Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.[105,106] 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.[107]

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

	Daily dose	Aurobindo	Matrix
Eligibility restrictions		None	None
FTC 200mg capsule	1	**67 (0.183)**	**79 (0.217)**

Products included in the List of WHO prequalified Medicinal Products (as of December 2009) are in **bold**.

Spotlight on access issues:

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

According to the WHO treatment guidelines, "FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus and has the same resistance profile."[111]

The new WHO 2009 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.[375]

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.[108]

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, in return for the payment of a 5% royalty.[109]

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

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

The Paediatric AIDS Working Group at WHO has given "important" priority to the development of a 35mg tablet.[110]

LAMIVUDINE (3TC)

General information

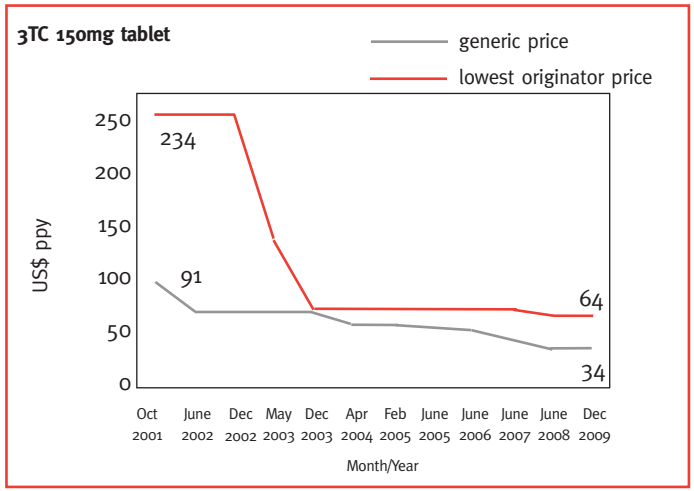
- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults and adolescents, and for first-line only for children (WHO 2006 guidelines)[142]
- Originator company and product brand name: GlaxoSmithKline (GSK), Epivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 1995.[143]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[144]
- World sales of originator product: 2008: US$ 225 million; 2007: US$ 309 million; 2006: US$ 398 million; 2005: US$ 398 million; 2004: US$ 549 million.[145,146,147]
- The basic patent on emtricitabine (FTC) and 3TC was filed by IAF Biochem in 1990 and is due to expire in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.[148,149]
- GSK obtained a license from IAF to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which are due to expire around 2012.[150]
- GSK also applied for a new formulation patent in 1998. This patent was granted in Brazil, China and in ARIPO countries.[151]

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

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
Eligibility restrictions		see annex 2	None	None	None	None	None
3TC 150mg tablet	2	**64 (0.087)**	**39 (0.053)**	**35 (0.048)**	**34 (0.046)**	**39 (0.054)**	**37 (0.050)**
3TC 300mg tablet	1		**24 (0.067)**	41 (0.113)	**34 (0.092)**		
3TC 10mg/ml oral solution	10ml	**84 (0.023/ml)**	**29 (0.008/ml)**	**37 (0.010/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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold**.



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

As of December 2009, there were nine generic sources of 3TC 150mg listed on the WHO List of Prequalified Medicinal Products and the lowest -priced product on the List is shown here.

Spotlight on access issues:

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.

The 2009 revision of the WHO guidelines recommend using TDF with either emtricitabine (FTC) or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.[375]

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

In China, where GSK still owns exclusive rights on 3TC, the price of the medicine remains very high, at around US$ 1,839 per patient per year. GSK is using its monopoly rights to block local production or importation of more affordable generic versions of 3TC.

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

Generic manufacturers have been developing both double and triple fixed-dose combinations containing 3TC. As of December 2009 there were four paediatric triple FDCs containing 3TC listed in the WHO Prequalification List of Medicinal Products.

To give clinicians flexibility in prescribing ARV regimens, there is a need for a single simple adapted formulation of 3TC. The Paediatric AIDS 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.[152]

STAVUDINE (d4T)

General information

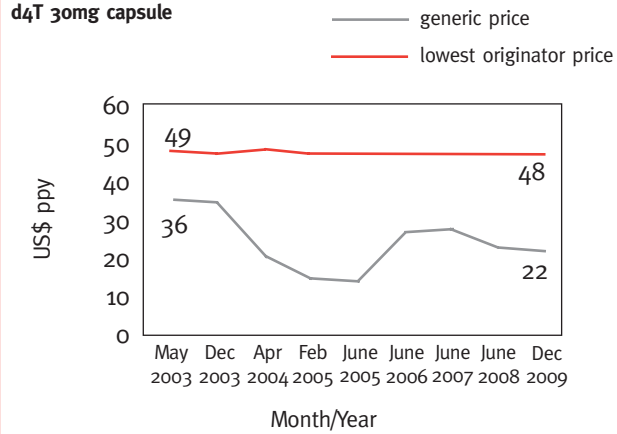
- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first-line for adults, adolescents and children (WHO 2006 guidelines).[236,237]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to 30mg for all weight categories of patients.[155]
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- First approval by U.S. Food and Drug Administration (FDA): December 1994.[238]
- Included in the 16th Edition WHO Model List of Essential Medicines (EML).[239]
- World sales of originator product: 2006: US$ 155 million; 2005: US$ 216 million; 2004: US$ 272 million; 2003: US$ 354 million. After 2006, there are no sales figures listed in the company's annual report.[240,241]
- d4T was the result of U.S. public sector research. It was originally synthesised by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.[242] 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.[243] This patent should have expired in December 2007, but the protection was extended until the end of 2008 in the U.S. and until 2011 in most European countries. BMS markets d4T under a marketing and distribution license from Yale University.
- Patents have expired in most countries at this point.

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

	Daily dose	Bristol-Myers Squibb		Aurobindo (CF)	Cipla (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
		Category 1	Category 2					
Eligibility restrictions		see annexes 2 and 7		None	None	None	None	None
d4T 15mg capsule	--	**(0.082)**	**(0.093)**	**(0.029)**	(0.024)			
d4T 20mg capsule	--	**(0.089)**	**(0.093)**	**(0.030)**	(0.025)			
d4T 30mg capsule	2	**48 (0.066)**	**68 (0.093)**	**22 (0.030)**	26 (0.035)	**24 (0.033)**	**26 (0.035)**	**22 (0.030)**
d4T 1mg/ml powder for syrup	20ml	**51 (0.007/ml)**	**58 (0.008/ml)**	**66 (0.009/ml)**	**44 (0.006/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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold.**



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

As of December 2009, there were six generic sources of d4T 30mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine (AZT) or tenofovir (TDF)-based first-line regimens.[375]

Patents Yale University did not apply for patents in most developing countries except for South Africa. Therefore, generic manufacturers from countries with manufacturing capacity, such as Brazil, China, India or Thailand could legally manufacture and export affordable generic versions of d4T. In South Africa, where BMS marketed d4T under an exclusive license from Yale, the drug was 34 times more expensive than generic versions available in other countries. This prompted a patent controversy in March 2001, particularly as the medicine had been developed with public funds. After pressure from researchers, students, and access advocates, Yale renegotiated its license with BMS to allow the importation of more affordable generic versions of d4T to South Africa.[244]

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, two d4t-containing triple FDCs are listed on the WHO List of Prequalified Medicinal Products.

TENOFOVIR DISOPROXIL FUMARATE (TDF)

General information

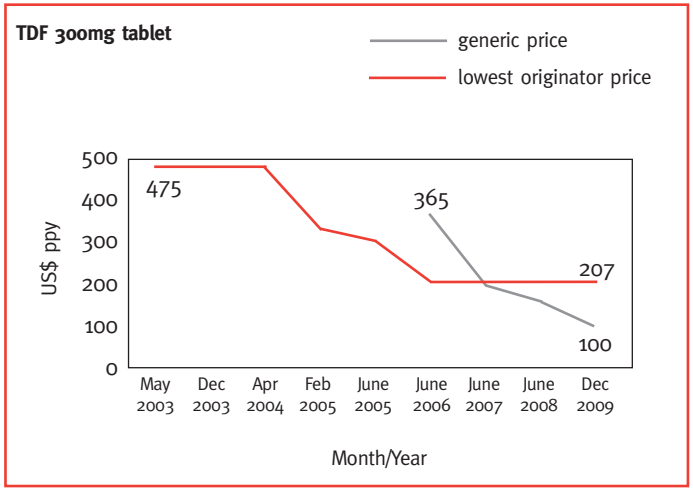
- Therapeutic class: nucleotide reverse transcriptase inhibitor (NtRTI).
- Indicated for first- and second-line for adults and adolescents (WHO 2006 guidelines).[246,247]
- Originator company and product brand name: Gilead, Viread.
- First approval by U.S. Food and Drug Administration (FDA): October 2001.[248]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[249]
- World sales of originator product: 2008: US$ 621 million; 2007: US$ 613 million; 2006: US$ 689 million; 2005: US$ 778 million; 2004: US$ 783 million.[250,251,252,253,254]
- 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.[255] Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997.[256] and for the fumarate salt of tenofovir disoproxil in 1998.[257] These are due to expire in 2017 and 2018, respectively. In addition, Gilead and BMS have applied for patents on fixed-dose combinations of TDF/FTC and TDF/FTC/EFV which, if granted in developing countries, will expire not earlier than 2024 and 2026 respectively.[258,259]

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

	Daily dose	Gilead		Aurobindo	Cipla (CF)	Matrix (CF)	Strides (CF)
		Category 1	Category 2				
Eligibility restrictions		see annexes 2 and 9		None	None	None	None
TDF 300mg tablet	1	**207 (0.567)**	**365 (1.000)**	**116 (0.317)**	**100 (0.275)**	**116 (0.317)**	149 (0.408)

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold**.



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

As of December 2009, there were three generic sources of TDF 300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

There has been a 73% decrease in the generic price since 2006, and a 56% decrease in the lowest originator price since 2003.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of its long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens. It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill, once a day. While the price today is still higher than a d4T-containing regimen, there is a need to generate greater demand which will, in turn, increase the competition needed to further decrease prices.[375]

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

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

For HIV patients requiring treatment for hepatitis B, the first- and second-line treatment should contain TDF and either 3TC or FTC.

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

Patents Gilead has applied for patents related to TDF in many developing countries, including India, Brazil and China. In Brazil and India, these patent applications have been opposed by civil society groups, as well as by some generic manufacturers.

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. The patents were rejected on the grounds that they lack an inventive step - they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law. Further, combinations of known molecules are not patentable under Indian patent law.[260,261,262]

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

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

Following oppositions (by members of Indian and Brazilian civil society) to the grant of its patents in India, 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 pre-defined list of countries, against the payment of a 5% royalty.[263]

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$ 927 per patient per year, over ten times the best available generic price.

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 currently not approved for children younger than 18 years in the U.S. Gilead is currently sponsoring two Phase III trials, the first involving adolescents (12-18 years) and the second involving children (2-12 years), using an oral powder formulation. Results from these studies are expected in 2010 and will contribute to the urgent need for dosing information and information on medium- and long-term toxicity in children.

In March 2009, U.S. FDA granted TDF an Orphan Drug designation for treatment of paediatric HIV infections.[370] Gilead is now entitled to seven years of marketing exclusivity for the designated paediatric indication, tax credits for clinical research and can apply for grants to defray the cost of clinical trials.[371]

ZIDOVUDINE (AZT or ZDV)

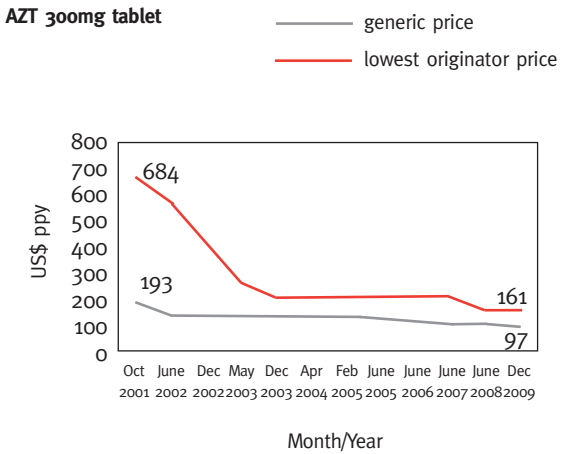
General information

- Therapeutic class: nucleoside reverse transcriptase inhibitor (NRTI).
- Indicated for first- and second-line for adults, adolescents and children (WHO 2006 guidelines).[320,321]
- Originator company and product brand name: GlaxoSmithKline (GSK), Retrovir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): March 1987.[322]
- Included in the 16th Edition of the WHO Model List of Essential Medicines (EML).[323]
- World sales of originator product: 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.[324,325]
- AZT was first discovered in 1964 as an anti-cancer medicine. The U.S. National Institutes of Health did the majority of the research that showed the drug's effectiveness as an antiretroviral. Glaxo Wellcome filed for patents on AZT for the treatment of AIDS and brought the drug onto the market in 1987 as one of the most expensive ever sold. Patents have expired in most countries at this point.

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

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Matrix (CF)	Ranbaxy
Eligibility restrictions		see annex 2	None	None	None	None
AZT 300mg tablet	2	**161 (0.221)**	**110 (0.150)**	**97 (0.133)**	**97 (0.133)**	**99 (0.135)**
AZT 100mg capsule	--	**(0.122)**	**(0.092)**	**(0.050)**		
AZT 250mg capsule	--	**(0.276)**				
AZT 10mg/ml syrup	20ml	**234 (0.032/ml)**	**73 (0.010/ml)**	**80 (0.011/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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold.**



Evolution of the lowest price quoted for eligible developing countries since 2001:
As of December 2009, there were seven generic sources of AZT 300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of its long term irreversible side effects and to move towards zidovudine or tenofovir (TDF)-based first-line regimens.[375]

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

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

Generic manufacturers have been developing both double and triple paediatric fixed-dose combinations including AZT. Today, however, there are four paediatric FDCs containing AZT that are listed on WHO Prequalification List of Medicinal Product. To give clinicians flexibility in prescribing ARV regimens, there is a need for a simple adapted formulation of AZT. The Paediatric AIDS Working Group of WHO has given “important” priority to the development of a 60mg tablet. Today there is one generic version of AZT 60mg which is prequalified by WHO.[326]

General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, for adults and adolescents (WHO 2006 guidelines).[50]
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approval by U.S. Food and Drug Administration (FDA): 20 June 2003.[51]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[52]
- World sales of originator product for 2008: US$ 1.29 billion; 2007: US$ 1.12 billion; 2006: US$ 931 million; 2005: US$ 696 million; 2004: US$ 369 million; 2003: US$ 81 million.[53,54,55,56]
- The basic patent was filed in April 1997 by Novartis and is expected to expire in April 2017.[57] Bristol-Myers Squibb is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998[58] and on a process for preparing the bisulfate salt and novel forms in 2005.[59]

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

	Daily dose	Bristol-Myers Squibb		Emcure (CF)
		Category 1	Category 2	
Eligibility restrictions		see annexes 2 and 7		none
ATV 100mg capsule	3*			**373 (0.341)**
ATV 150mg capsule	2*	**353 (0.484)**	**431 (0.590)**	**318 (0.435)**
ATV 200mg capsule	--	(0.602)	(0.743)	**(0.518)**

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

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

Products included in the WHO list of Prequalified Medicinal Products (as of December 2009) are in **bold**.

Note: BMS second category pricing is provided in South African Rand (ZAR). These were converted to US$ on the date the prices were received, hence fluctuations in the US$/ZAR rate will impact these prices.

Spotlight on access issues:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). Of the two, ATV is the most patient-friendly PI, as it requires the patient to take only two 150mg pills once a day.[375]

ATV, like all PIs (with the exception of nelfinavir (NFV)), requires 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.

The required addition of RTV as a booster must also be considered in the final cost of using ATV. As ATV is one of the two PIs recommended by WHO, there is an urgent need for generic manufacturers to supply a heat-stable ATV/r fixed-dose combination.

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 patent applications are still under examination, civil society organisations filed a pre-grant opposition to Novartis's basic patent application on the grounds of lack of novelty,[60] but the other patent applications warrant additional pre-grant oppositions.

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

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

BMS has a separate agreement with Emcure that covers India.[61] Licensing agreements in India should not be necessary if patent oppositions are successful. If the patent is granted, the only alternative for India and other countries will be to use compulsory licenses to enable unrestricted competition from generic manufacturers, in order to bring prices down and increase access.

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$ 1,591 per patient per year, which is prohibitive for many of these countries.[62]

Paediatrics In March 2008, ATV was approved for use in children between six and 18 years of age. In 2008, WHO recommended early treatment for all HIV-positive children, and children who have been exposed to nevirapine either through their mother or through a single dose in a PMTCT programme. WHO recommends these children should be started on a PI-based regimen.[63] Today, the only option for these children is the LPV/r formulation. To simplify treatment for all children, there is an urgent need for studies on ATV to be completed down to infants, and child-adapted formulations to be made available.

DARUNAVIR (DRV)

General information

- Therapeutic class: protease inhibitor (PI).
- 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 (adults). It is also indicated in developed countries for treatment-naïve patients.[65]
- Originator company and product name: Tibotec (a division of Johnson&Johnson), Prezista.
- First approved by the U.S. Food and Drug Administration (FDA): 23 June 2006.[66]
- Not included in the WHO Model List of Essential Medicines (EML).[67]
- Darunavir basic patent applied for by Searle and Monsanto in August 1993,[68] and due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to darunavir in 1999[69] and licensed them to Tibotec for development.[70] Tibotec later applied for patents related to improved forms and combinations of darunavir.[71,72]

Price information:

Prices in US$ quoted by companies for eligible developing countries

	Daily dose	Tibotec
Eligibility restrictions		see annex 2
DRV 300mg tablet	4*	1095 (0.750)

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

Spotlight on access issues:

In December 2009, WHO released new recommendations which for the first time call for the need of third-line therapy. As many studies are ongoing, drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir, etravirine and raltegravir.[375]

Tibotec signed a royalty-free, non-exclusive license agreement with South African firm Aspen on 4 April 2007. This grants Aspen the right to register, package and distribute darunavir (DRV) in sub-Saharan Africa.[73] This agreement excludes other low- and middle-income countries, for which the price paid in wealthy countries, at over US$ 12,000 per patient per year, is prohibitive.[74]

In Brazil, DRV was included in the government's guidelines in 2008, but at US$ 8,018 per patient per year, it is very expensive.

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.

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

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

In addition, a number of patents related to DRV exist in Brazil.

Paediatrics In December 2008, DRV was approved for use in children between six and 18 years of age. Paediatric formulations are available, but Tibotec has not provided price information for those products.

FOSAMPRENAVIR (FPV or f-APV)

General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, for adults (WHO 2006 guidelines)[129].
- Originator company and product brand name: GlaxoSmithKline and Vertex Pharmaceuticals, Lexiva. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approved by the U.S. Food and Drug Administration(FDA): 20 October 2003.[130]
- Not included in the WHO Model List of Essential Medicines (EML).[131]
- Basic patent applied for by Vertex Pharmaceuticals in March 1998,[132] and due to expire in 2018. Fosamprenavir, a phosphate ester prodrug of amprenavir,[133] was developed and launched by GSK, under license from Vertex.

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

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

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

Spotlight on access issues:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As fosamprenavir (FPV) was not identified as one of the priority products, its use will be limited in the developing world.[375]

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.[135]

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.

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

Patents Patent applications have been filed for in many developing countries. In Brazil, the basic patent has been rejected by the patent office, but there is a patent on the calcium salt that will expire in 2019. In China, South Africa and OAPI countries,[134] both of these patents have been granted. In India, patent applications on the FPV salts, including calcium, have been filed and are pending review by the patent office.

There are no generic formulations of this product available today.

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

INDINAVIR (IDV)

General information

- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line for adults (WHO 2006 guidelines)[136]
- Originator company and product brand name: Merck, Crixivan.
- First approval by U.S. Food and Drug Administration (FDA): March 1996.[137]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML)[138]
- There are no sales figures for this product listed in the company annual report.
- The basic patent was filed for by Merck in 1991 and is due to expire in 2012 in countries granting 20-year patents.[139]

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

	Daily dose	Merck		Aurobindo	Cipla	Ranbaxy
		Category 1	Category 2			
Eligibility restrictions		see annexes 2 and 10		None	None	None
IDV 400mg capsule	4*	**394 (0.270)**	**686 (0.470)**	365 (0.250)	422 (0.289)	**426 (0.292)**

*The dose of IDV must be boosted with RTV 100mg twice a day.
Products included in the WHO list of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.

Spotlight on access issues:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).[64] As IDV was not identified as one of the priority products, its use will be limited in the developing world.[375]

The main concern was that at a standard dose of 800mg IDV with 100mg ritonavir (RTV) twice a day, it was less well tolerated than other PIs, particularly in hot climates.[141] There have been some small studies to support a lower dose of IDV + RTV 400 + 100mg twice a day with the aim to reduce toxicity. The U.S. FDA has also approved the use of IDV at 800mg every eight hours without RTV.

IDV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with 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.

The required addition of RTV as a booster must also be considered in the final cost of using IDV. Some generic manufacturers have stopped production of IDV, or only manufacture it for specific orders, because of a decrease in demand for this product.

Paediatrics The optimal dosing regimen for the use of IDV in paediatric patients has not been established and no paediatric formulation exists.[140]

LOPINAVIR/RITONAVIR (LPV/r)

General information

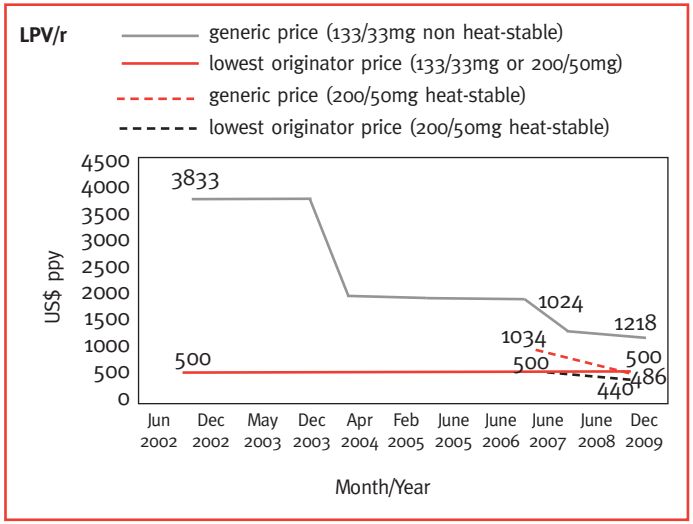
- Therapeutic class: boosted Protease Inhibitor (PI) in a double fixed-dose combination.
- Indicated for second-line, for adults, adolescents and children (WHO 2006 guidelines).[172,173]
- First approval by U.S. Food and Drug Administration (FDA): September 2000 (soft-gel capsules); October 2005 (heat-stable tablets).[174]
- Originator company and product brand name: Abbott Laboratories, Kaletra, Aluvia.
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[175]
- World sales of originator product: 2008: US$ 1.47 billion; 2007: US$ 1.32 billion; 2004: US$ 897 million; 2003: US$ 754 million; 2002: US$ 551 million; 2001: US$ 292 million.[176,177]
- Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.[178]
- In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997[179] which are due to expire in 2017. An application for a patent on the heat-stable tablet formulation was also filed in 2004,[180] 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)	Matrix (CF)
		Category 1	Category 2			
Eligibility restrictions		see annexes 2 and 8		None	None	None
LPV/r 133/33mg soft gel capsule	6	**500 (0.228)**	**1000 (0.457)**		1218 (0.556)	
LPV/r 200/50mg tablet (heat-stable)	4	**440 (0.301)**	**1000 (0.685)**	**511 (0.350)**	486 (0.333)	**486 (0.333)**
LPV/r 80/20mg/ml oral solution	4ml	**176 (0.121/ml)**	**400 (0.274/ml)**			
LPV/r 100/25mg tablet (heat-stable)	3	**165 (0.151)**	**376 (0.343)**	**329 (0.300)**		**228 (0.208)**

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **bold**.



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

As of December 2009, there were two generic sources of lopinavir/ritonavir 200/50mg listed on the WHO List of Prequalified Medicinal Products. The lowest available generic price for both the heat-stable tablet and soft-gel capsule are considered for the graph.

The generic price has decreased by 53% since 2007.

Spotlight on access issues:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).[375]

The heat-stable formulation of LPV/r manufactured by Abbott and Indian generic companies (Aurobindo, Cipla, Matrix) is now marketed in developing countries. In comparison to the older, soft-gel capsule formulation, the new formulation has a lower pill count (reducing the burden from six to four pills per day), there is no need for refrigeration, and there are no dietary restrictions.

The entry of generic manufacturers is having a positive effect on the market, and prices are declining. The Clinton Foundation's most recent announcement has some generic manufacturers offering prices of US$ 470 ppy. For the first time, the quoted generic price is lower than the originator price for this fixed-dose combination.

Since the initial online publication of Untangling the Web in December 2009, Abbott has indicated a price decrease for LPV/r 200/50mg from US$ 500 to US$ 440 ppy, bringing the price below that of generic manufacturers.

Patents In India, Abbott has applied for several patents on the solid dosage formulation and polymorph forms of lopinavir (LPV), ritonavir (RTV) and on the heat-stable combination of LPV/r, a number of which have been opposed by civil society organisations[181] and generic companies. Following a pre-grant opposition to the application related to the soft-gel formulation of LPV/r, the company withdrew the application. Other oppositions are pending decisions by the Indian patent office.

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

In Thailand, where Abbott holds patents, the price of LPV/r was US$ 2,200 per patient per year (ppy) in 2007. In January 2007, the Ministry of Public Health issued a compulsory license to import more affordable generic versions of the drug from India.[182] Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies and Abbott's response was to withdraw all registration applications in Thailand for its new products, including the heat-stable LPV/r. Thailand today imports generic LPV/r from India for US$ 748 ppy.[183]

In response to Thailand's compulsory license, Abbott reduced the price for 40 middle-income countries for both the soft gel and the heat-stable version to US$ 1000 ppy, including Brazil which at the time was paying US$ 1,380.[373]

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 which it must be stored below 25°C for no more than six weeks. Furthermore, the solution consists of 42% alcohol and has a very unpleasant taste. A heat-stable sprinkle in a paediatric dose is under development by generic companies.

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

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

There is an urgent need for a more adapted formulation for young children.

NELFINAVIR (NFV)

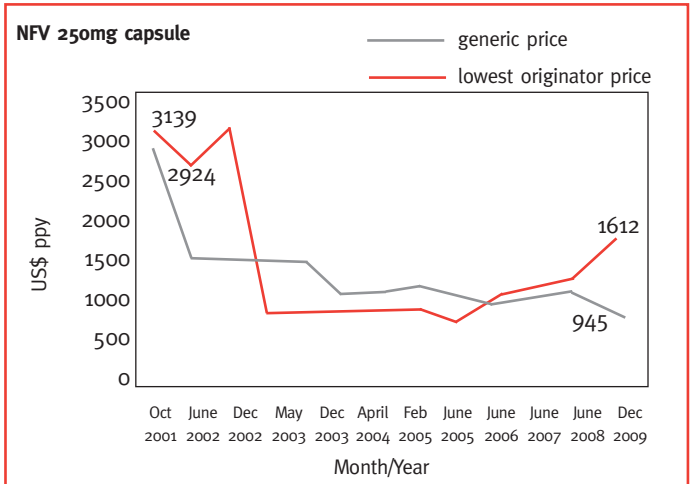
General information

- Therapeutic class: protease inhibitor (PI).
- Indicated only for second-line in adults, adolescents and children (WHO 2006 guidelines).[194,195]
- Originator company and product brand name: Roche, Viracept.
- First approval by U.S. Food and Drug Administration (FDA): 14 March 1997.[196]
- Deleted from the 16th edition of the WHO Model List of Essential Medicines (EML).[197]
- World sales of originator product: 2004: US$ 259 million. After 2004, there are no sales figures listed in the company's annual report.[198]
- Basic patent applied for in 1994 by Agouron Pharmaceuticals Inc.,[199] 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, Inc. NFV is supplied by Roche outside U.S., Canada and Japan.[200]

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

	Daily dose	Roche		Cipla
		Category 1	Category 2	
Eligibility restrictions		see annex 2		None
NFV 250mg tablet	10	**1612 (0.442)**	**2501 (0.685)**	945 (0.259)
NFV 50mg/g oral powder	24g	**2189 (0.250/g)**	**2533 (0.289/g)**	

Products included in the WHO list of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, 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 have been converted to US$ on the date received. Fluctuations in the US$/CHF rate will thus have an impact on prices used in the graph.

NELFINAVIR (NFV)

Spotlight on access issues:

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

The large pill burden (10 tablets a day for an adult) and 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 by-product of the manufacturing process and a known carcinogen in animals. Roche's marketing licence for NFV was suspended in Europe and the WHO prequalification project temporarily suspended the product. In September 2007, the suspensions were lifted and marketing licences reinstated.[201]

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

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

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

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

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

RITONAVIR (r or RTV)

General information

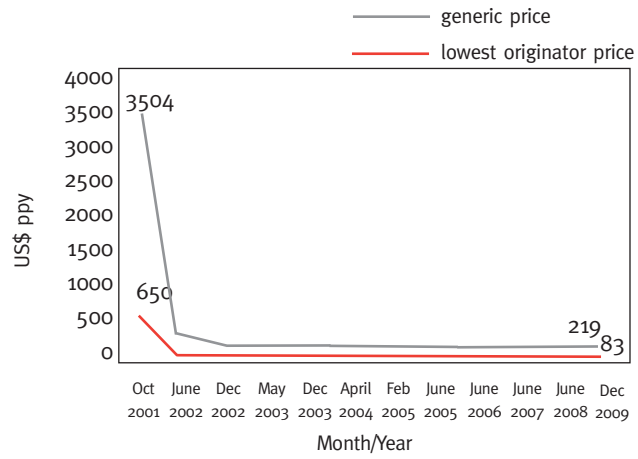
- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line as a booster, for adults, adolescents and children (WHO 2006 guidelines).[220,221]
- Originator company and product brand name: Abbott Laboratories, Norvir.
- First approval by U.S. Food and Drug Administration (FDA): March 1996 for the oral solution and 29 June 1999 for capsules.[222]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[223]
- World sales of originator product: 2004: US$ 194 million; 2003: US$ 93 million; and 2002: US$ 122 million.[224]
- Basic patent applied for by Abbott in 1993.[225,226,227] 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	Strides
Eligibility restrictions		see annexes 2 and 8	None	None
RTV 100mg capsule	2	**83 (0.114)**	313 (0.429)	219 (0.300)
RTV 80mg/ml oral solution	--	**(0.093/ml)**		

Products included in the WHO list of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.

Ritonavir 100mg capsule (non heat-stable)



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

As of December 2009, there was no generic source of RTV listed on the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown here.

RITONAVIR (r or RTV)

Spotlight on access issues:

Ritonavir (RTV) is of crucial importance for the scaling-up and management of second-line treatment, as all protease inhibitors, (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 developing countries.

Abbott has developed a heat-stable fixed-dose combination of lopinavir 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 filed for registration of the heat-stable version of RTV with U.S. FDA and EMEA. The development and marketing of a heat-stable RTV formulation would be critical to eliminating the heat-stable boosted PI monopoly that Abbott currently has with LPV/r.

Patents Although the basic patent disclosing RTV could not be applied for in India, Abbott's original patent applications and divisional applications on new forms of RTV are pending before the Indian patent office. A pre-grant opposition to an application related to a polymorph of RTV was filed by civil society organisations in India in September 2006.[228]

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

The Paediatric Antiretroviral Working Group of WHO has given "important" priority to the development of a 25mg heat-stable RTV tablet.[229]

SAQUINAVIR (SQV)

General information

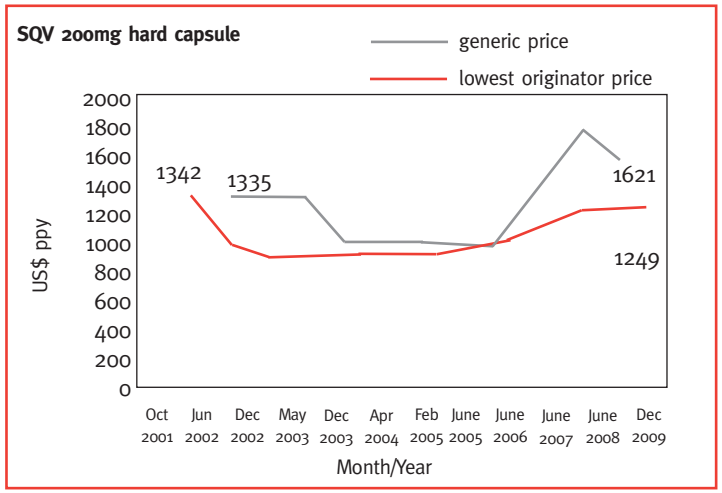
- Therapeutic class: protease inhibitor (PI).
- Indicated for second-line, to be used boosted by ritonavir, for adults, adolescents and children (WHO 2006 guidelines).[230]
- Originator company and product brand name: Roche, Invirase.
- First approval by U.S. Food and Drug Administration (FDA): December 1995.[231]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[232]
- The basic patent was applied for by Roche in 1990[233] and is due to expire in 2010.
- The patent related to oral dosage form was applied by Roche in 2004 and is due to expire in 2024.[234]

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

	Daily dose	Roche		Cipla
		Category 1	Category 2	
Eligibility restrictions		see annex 2		None
SQV 200mg hard capsule	10*	**1249 (0.342)**	**2501 (0.685)**	1621 (0.444)
SQV 500mg tablet	4*	**1146 (0.785)**	**2499 (1.712)**	

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

Products included in the WHO list of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there was no generic source of SQV listed on the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown here.

Spotlight on access issues:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As saquinavir (SQV) was not identified as one of the priority products, its use in the developing world will be limited.[375]

SQV/r appears to be slightly less potent than the other boosted PIs and in the original formulation has a high pill count (10 capsules).[235]

In 2004, Roche marketed in the U.S. a 500mg tablet of SQV that reduced the pill count from 10 tablets to four. While this new formulation should improve adherence, it is only registered and marketed in selected developing countries.

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

SQV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's 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.

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

Patents The basic patent was rejected in Brazil. But the patent related to the oral dosage form was granted in India and in OAPI countries.

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.[312]
- Originator company and product brand name: Boehringer Ingelheim, Aptivus.
- First approved by the U.S. Food and Drug Administration (FDA): 23 June 2005.
- Not included in the WHO Model List of Essential Medicines (EML).[313]
- Basic patent applied for by Upjohn in May 1995,[314] 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.[315,316] 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:

In December 2009, WHO recommended that for second-line therapy, the preferred protease inhibitors to be taken in combination with two NRTIs are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As tipranavir (TPV) was not identified as one of the priority products, its use in the developing world will be limited.[375]

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

TPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's monopoly on RTV and the temperature sensitivity of current formulations of RTV may limit the use of this product in the developing world. TPV capsules also require refrigeration until dispensing.

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

Patents TPV patents have been filed for 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), which has to give "prior consent" for any patent application related to a medicine, has advised for the rejection of the basic patent application.[317]

In early 2007, civil society expressed concerns over the delays to the registration procedure of TPV in Brazil (the medicine had been tested in Brazilian patients in 14 research centres since February 2004, but the drug was not actually registered in the country). After considerable civil society pressure, the registration was eventually filed with ANVISA at the end of February 2008, almost three years after U.S. FDA and EMEA approvals. The intervention by Brazilian civil society was partly based in response to suspicions that Boeringer Ingelheim did not want to register the product in the country, unless they had the guarantee that the patent would be granted by the patent office.[318,319]

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

General information

- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first-line for adults, adolescents and children.[39,40]
- Originator company and product brand name: GlaxoSmithKline (GSK), Kivexa (EU), Epzicom (U.S.). In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.[41]
- 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.[42]
- World sales of originator product: 2008: US$ 721 million; 2007: US$ 641 million; 2006: US$ 475 million; 2005: US$ 233 million.[43,44,45,46]
- Most patents on abacavir (ABC) or lamivudine (3TC) also affect this combination. In addition, GSK applied for patents more specifically related to the combination.[47] The patent expiry dates related to this combination are 2016 in the U.S. and 2019 in EU.[48]

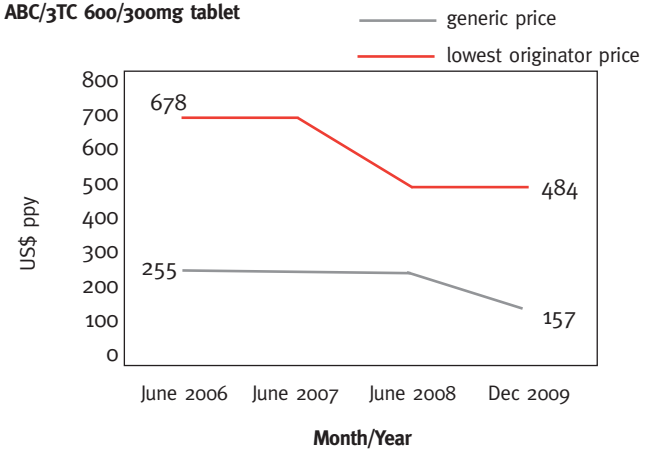
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug product cards.

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

	Daily dose	GSK	Aurobindo (CF)	Cipla	Matrix (CF)
Eligibility restrictions		see annex 2	None	None	None
ABC/3TC 600/300mg tablet	1	484 (1.326)	**157 (0.429)**	152 (0.417)	
ABC/3TC 60/30mg tablet	4		**194 (0.133)**		244 (0.167)

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there was one generic source of ABC/3TC 600/300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

There has been a decrease of 38% in the generic price since 2006.

Spotlight on access issues:

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

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

Paediatrics The Paediatric Antiretroviral Working Group at WHO classed the development of a paediatric formulation of ABC/3TC fixed-dose combination a "high" priority.[49]

Yet GSK does not produce a fixed-dose combination of these drugs for children – even though the same is produced for adults. Nevertheless for children who need this combination, there are now two generic sources which appear on the WHO List of Prequalified Medicinal Products.

General information

- Therapeutic class: double fixed-dose combination of two NRTIs.
- Indicated for first-line for adults, adolescents and children (WHO 2006 guidelines).[153,154]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.[155]
- 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.[156]
- Not included in the WHO Model List of Essential Medicines (EML) as a fixed-dose combination, but the individual drugs are included in the EML.[157]
- Individual patents on lamivudine (3TC) or stavudine (d4T) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of both medicines in combination, or to the FDC.

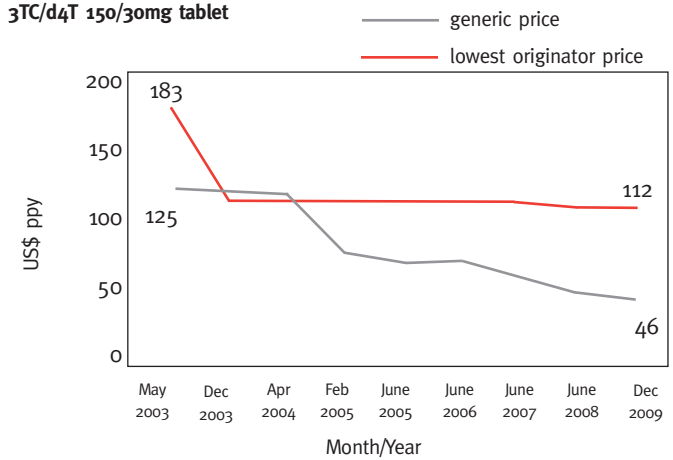
For information on the individual ARVs contained in this fixed-dose combination, please refer to the individual drug profiles.

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

	Daily dose	Aurobindo (CF)	Cipla (CF)	Matrix (CF)	Ranbaxy (CF)	Strides (CF)
Eligibility restrictions		None	None	None	None	None
3TC/d4T 150/30mg tablet	2	**53 (0.072)**	**50 (0.068)**	**49 (0.067)**	**55 (0.075)**	**46 (0.063)**
3TC/d4T 30/6mg dispersible tablet	4		**47 (0.032)**			
3TC/d4T 60/12mg dispersible tablet	2		**40 (0.055)**			

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were six generic sources of 3TC/d4T 150/30mg on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

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

There has been a 39% decrease in the originator price and a 63% 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.

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens. We can therefore expect to see a decrease in the use of this formulation in the future.[375]

Patents Generic companies in certain developing countries were able to develop these fixed-dose combinations because patents on the individual products did not exist. The FDC is not available in developed countries or in countries such as China, however, where one or both medicines is under patent.

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

The Paediatric Antiretroviral Working Group at WHO classed the development of a paediatric formulation of 3TC/d4T fixed-dose combination an "urgent" priority.[368] For children who need this double 3TC/d4T FDC, there are two generic products which are listed on the WHO List of Prequalified Medicinal Products.

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).[164,165]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.[166]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML) – only the d4T 30mg presentation.[167]
- 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.[168]
- Individual patents on lamivudine (3TC), stavudine (d4T) or nevirapine (NVP) also affect this combination. In addition, other patents may have been applied for more specifically relating to the use of the medicines in combination or to the fixed-dose combination. Cipla first developed the FDC and applied for patents in several African countries.

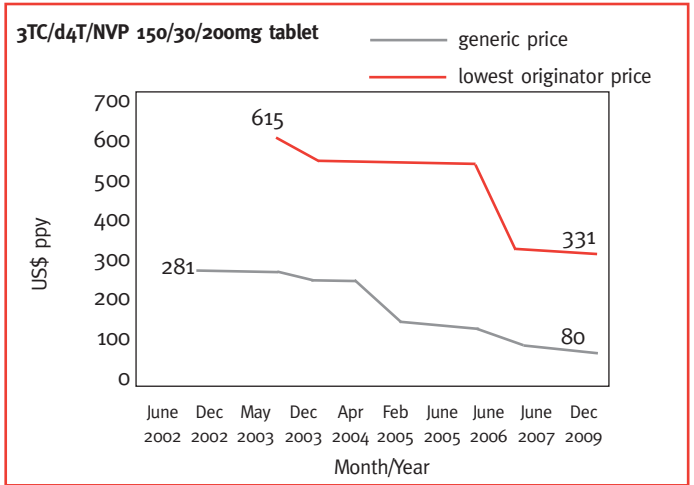
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug profiles.

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

	Daily dose	Aurobindo (CF)	Cipla (CF)	Emcure	Matrix (CF)	Ranbaxy	Strides (CF)
Eligibility restrictions		None	None	None	None	None	None
3TC/d4T/NVP 150/30/200mg tablet	2	**82 (0.113)**	**80 (0.110)**	**88 (0.121)**	**85 (0.117)**	**93 (0.128)**	**91 (0.125)**
3TC/d4T/NVP 30/6/50mg dispersible tablet	4		**61 (0.042)**				
3TC/d4T/NVP 60/12/100mg dispersible tablet	2		**55 (0.076)**				

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were eight generic sources of 3TC/d4T/NVP 150/30/200mg listed in the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

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

There has been a decrease of 72% 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.

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of its long-term irreversible side effects and develop a plan to move towards zidovudine (AZT) or tenofovir (TDF)-based first-line regimens. We can therefore expect to see a decrease in the use of this formulation in the future.[375]

Patents Cipla was able to develop this combination because none of the individual components were patented in India.

Many other generic manufacturers have followed suit in other developing countries, such as Thailand, where the medicines were not patented.

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

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

The Paediatric Working Group at WHO has now released clear guidance on the ideal strength of each of the individual ARVs in these fixed-dose combinations, and today there are two formulations listed on the WHO List of Prequalified Medicinal Products.[169]

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

General information

- Therapeutic class: two NRTIs + one NNRTI in a co-blister.
- Indicated for first-line for adults, adolescents and children (WHO 2006 guidelines).[159,160]
- WHO updated the 2006 guidelines to recommend a reduction in dose of d4T from 40 to 30mg for all weight categories of patients.[161]
- Not included in the WHO Model List of Essential Medicines (EML) as a co-pack, but the individual drugs are included in the EML.[162]
- 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.[163]
- Individual patents on lamivudine (3TC), stavudine (d4T) or efavirenz (EFV) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of the medicines in combination, or to the FDC.

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

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 tablets (Co-pack)	1 kit (3 tablets)	274 (0.751)	**345 (0.945)**	176 (0.483)

Products included in the WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.

Spotlight on access issues:

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine (AZT) or tenofovir (TDF)-based first-line regimens. We can therefore expect to see a decrease in the use of this formulation in the future.[375]

Generic companies in certain developing countries were able to develop this co-blister because patents on the individual components contained in the combination did not exist. This product is not available in developed countries or in China because of various patents on lamivudine (3TC), stavudine (d4T) and/or efavirenz (EFV).

General information

- Therapeutic class: one NtRTI + one NRTI in a double fixed-dose combination.
- Indicated for first-line and second-line for adults and adolescents (WHO 2006 guidelines).[266,267]
- Originator company and product brand name: Gilead, Truvada.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.[268]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[269]
- 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.[270]
- World sales of originator product: 2008: US$ 2.11 billion; 2007: US$ 1.59 billion; 2006: US$ 1.19 billion; 2005: US$ 568 million; 2004: US$ 68 million.[271]
- Most patents related to tenofovir (TDF) or to emtricitabine (FTC) also affect this combination. In addition, Gilead applied for patents specifically related to this combination in 2004, which are due to expire in 2024.[272]

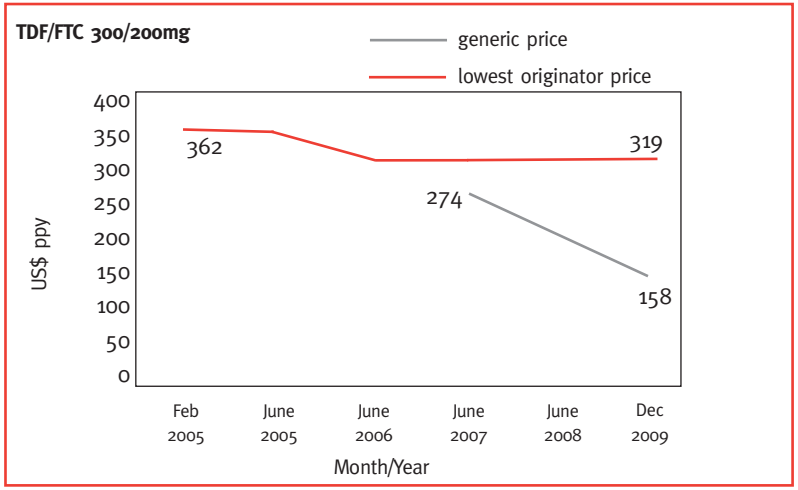
For information on the individual ARVs contained in this fixed-dose combination, please refer to the individual drug profiles.

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

	Daily dose	Gilead		Aurobindo (CF)	Cipla (CF)	Matrix (CF)
		Category 1	Category 2			
Eligibility restrictions		see annexes 2 and 9		None	None	None
TDF/FTC 300/200mg tablet	1	**319 (0.875)**	**548 (1.500)**	**164 (0.450)**	152 (0.417)	**158 (0.433)**

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were two generic sources of TDF/FTC 300/200mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Since 2007, there has been a 45% decrease in the generic price.

Spotlight on access issues:

This combination is likely to be widely used in developing countries as a backbone in first- and second-line regimens. In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine (AZT) or tenofovir (TDF)-based first-line regimens.[375]

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

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

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

Today, there are two generic sources listed on the WHO List of Prequalified Medicinal Products.

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

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. The patents were rejected on the grounds that they lack an inventive step - they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law. Further, combinations of known molecules are not patentable under Indian patent law.[273,274,275]

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

The same is true in Brazil, where the government declared its public interest in TDF in April 2008, considering it to be an essential drug. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on 30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with ten generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.[276]

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$ 927 per patient per year, over ten times the best available generic price.

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.

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).[279,280]
- Originator company and product brand name: Gilead/Bristol-Myers Squibb/Merck, Atripla.
- First approval by U.S. Food and Drug Administration (FDA): July 2006.[281]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[282]
- 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.[283]
- World sales of the originator: 2008: US$ 1.572 billion; 2007: US$ 903 million; 2006, US$ 164 million (the product entered the market in the third quarter of the year).[284]
- Most patents related to tenofovir (TDF), emtricitabine (FTC), TDF/FTC or to efavirenz (EFV) also affect this combination. In addition, Gilead and BMS jointly applied for patents specifically related to this combination in 2006,[285,286] 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.
- This is the first one-pill-a-day fixed-dose combination, which makes it well-adapted to resource-poor settings.

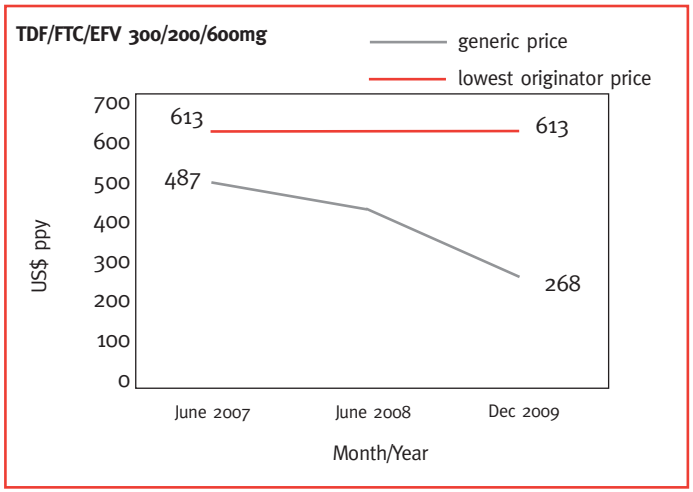
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug profiles.

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 annexes 2 and 10		None	None
TDF/FTC/EFV 300/200/600mg tablet	1	**613 (1.680)**	**1033 (2.830)**	268 (0.733)	268 (0.733)

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there was no generic source of TDF/FTC/EFV 300/200/600mg listed on the WHO List of Prequalified Medicinal Products. The lowest available generic price is shown here.

Since 2007, the generic price has decreased by 45%, while originator price has remained the same.

Spotlight on access issues:

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

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens. Efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on TB treatment.[375]

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

Today, there is one generic source which is tentatively approved by the U.S. FDA, but it is not prequalified by WHO.

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

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law. Further, combinations of known molecules are not patentable under Indian patent law.[287,288,289]

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

The same is true in Brazil, where the government declared its public interest in TDF in April 2008, considering it to be an essential drug. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on 30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with ten generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.[290]

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$ 927 per patient per year, over ten times the best available generic price.

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.

General information

- Therapeutic class: NtRTI + NRTI in a double fixed-dose combination.
- Indicated for first-line and second-line for adults and adolescents (2006 WHO guidelines).[292,293]
- Not included in the WHO Model List of Essential Medicines (EML) as a fixed-dose combination, but the individual drugs are included in the EML.[294]
- 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.[295]
- Most patents related to tenofovir (TDF) or to lamivudine (3TC) also affect this combination. In addition, other patents may have been applied for, more specifically related to the use of these medicines in combination, or to this specific FDC. Cipla applied for patents more specifically related to this combination.[296]

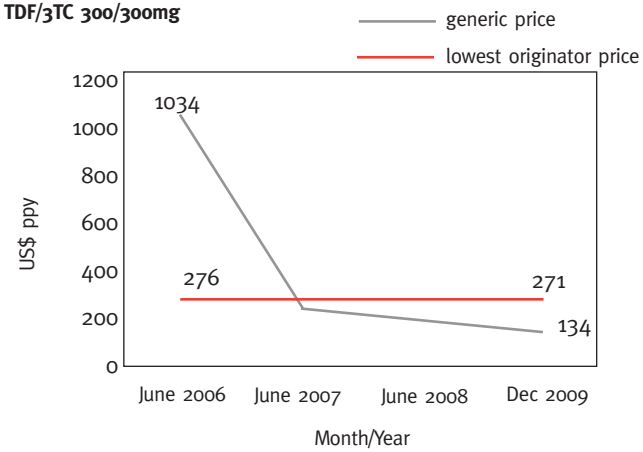
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug profiles.

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

	Daily dose	Cipla	Matrix (CF)
Eligibility restrictions		None	None
TDF/3TC 300/300mg tablet	1	134 (0.367)	**134 (0.367)**

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were two generic sources of TDF/3TC 300/300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

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

Since 2006, the generic price has dropped by 87%.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.[375]

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

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

For HIV patients requiring treatment for hepatitis B, the first- and second-line treatment should contain TDF and 3TC or FTC.

Today there are two generic sources of TDF/3TC listed on the WHO List of Prequalified Medicinal Products.

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

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law. Further, combinations of known molecules are not patentable under Indian patent law.[297,298,299]

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

The same is true in Brazil, where the government declared its public interest in TDF in April 2008, considering it to be an essential drug. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on 30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with ten generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.[300]

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$ 927 per patient per year, over ten times the best available generic price.

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.

General information

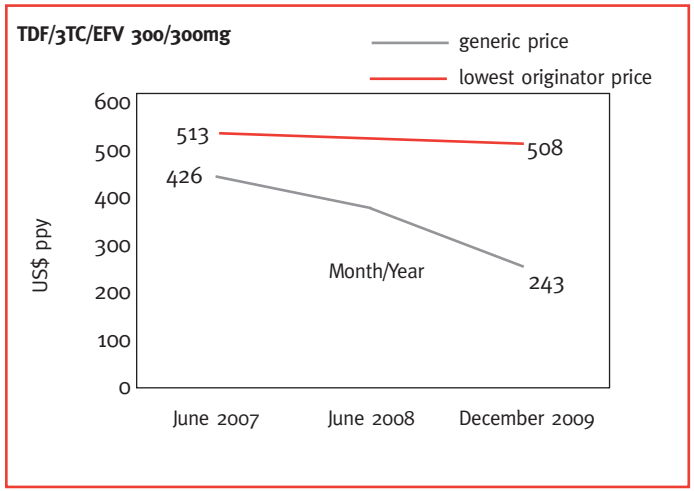
- Therapeutic class: one NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- Indicated for first-line for adults (WHO 2006 guidelines).[303,304]
- Not included in the WHO Model List of Essential Medicines (EML) as a fixed-dose combination, but the individual drugs are included in the EML.[305]
- 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.[306]
- Most patents related to tenofovir (TDF), lamivudine (3TC) or to efavirenz (EFV) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination, or to this specific FDC.

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

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

	Daily dose	Cipla	Matrix (CF)
Eligibility restrictions		None	None
TDF/3TC/EFV 300/150/600mg tablet (FDC)	1		243 (0.667)
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 2007:

As of December 2009, there was no generic source of TDF/3TC/EFV 300/300/600mg listed on the WHO List of Prequalified Medicinal Products. The lowest available generic price is therefore shown in the graph.

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

Since 2007, the generic price has dropped by 43%.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens. Efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on TB treatment.[375]

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

Today there is one generic source of TDF/3TC/EFV tentatively approved by the U.S. FDA but it is not yet listed on the WHO Prequalification List of Medicinal Products.

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

In a major victory for access to medicines, the Indian patent office rejected several patent applications relating to TDF in September 2009. The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law. Further, combinations of known molecules are not patentable under Indian patent law.[307,308,309]

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

The same is true in Brazil, where the government declared its public interest in TDF in April 2008, considering it to be an essential drug. The National Institute on Industrial Property (INPI) published the patent rejection for TDF on 30 June 2009. However, Gilead has also requested a divisional patent for the previously rejected patent.

Following oppositions to the grant of its patents in India, Gilead signed licensing agreements with ten generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's products to a limited pre-defined list of countries, against the payment of a 5% royalty.[310]

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$ 927 per patient per year, over ten times the best available generic price.

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.

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 for children (WHO 2006 guidelines).[329,330]
- Originator company and product brand name: GlaxoSmithKline (GSK), Combivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): September 1997.[331]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[332]
- 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.[333]
- World sales of the originator: 2008: US$ 713 million; 2007: US$ 888 million; 2006: US$ 1,042 million; 2005: US$ 1,150 million; 2004: US$ 1,125 million.[334,335,336,337,338]
- Most patents related to zidovudine (AZT) or to lamivudine (3TC) also affect this combination. In addition, GSK applied for patents specifically related to the use of AZT and 3TC in combination,[339] and for the tablet formulation of the FDC,[340] which are due to expire in 2012 and 2017, respectively.

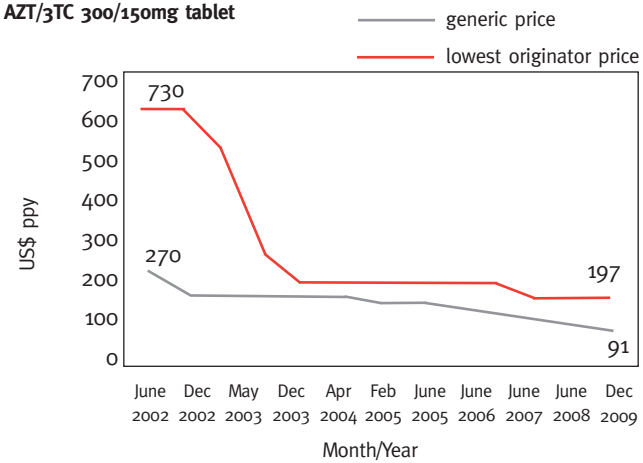
For information on the individual ARVs contained in this fixed-dose combination please refer to the individual drug profiles.

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

	Daily dose	GSK	Aurobindo (CF)	Cipla (CF)	Emcure	Matrix (CF)	Ranbaxy	Strides (CF)
Eligibility restrictions		see annex 2	None	None	None	None	None	None
AZT/3TC 300/150mg tablet	2	**197 (0.270)**	**122 (0.167)**	**117 (0.160)**	**91 (0.125)**	**122 (0.167)**	**124 (0.170)**	**146 (0.200)**
AZT/3TC 60/30mg tablet	4		**146 (0.100)**			**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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were nine generic sources of AZT/3TC 300/150mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

Competition among WHO prequalified sources continues, and has led to a steady decrease in prices of the originator product by 73% and the generic by 66% since 2001.

Spotlight on access issues:

There will be a continued need for this important FDC.

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long-term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.[375]

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

Patents Generic versions of this combination were developed in countries where neither of the molecules, nor their combination, were patented. However, the generic versions of the medicine produced in India came under threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination.

Civil society organisations in India opposed the patent application in March 2006,[341] which resulted in GSK communicating in August 2006 that patents specifically related to the fixed-dose combination were being withdrawn in all countries.[342]

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

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

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 difficult to administer. Today, there are two paediatric AZT/3TC FDC tablets listed on the WHO List of Prequalified Medicinal Products. The Paediatric Antiretroviral Working Group at WHO has classed the development of a paediatric AZT/3TC FDC as an “urgent” priority.[343]

General information

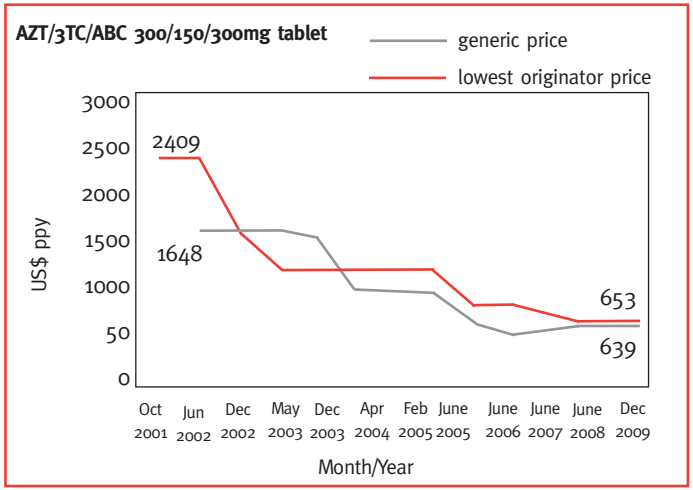
- Therapeutic class: three NRTIs in triple fixed-dose combination.
- Indicated for first-line for adults, adolescents and children (WHO 2006 guidelines).[350,351]
- The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.[352]
- Originator company and product brand name: GlaxoSmithKline (GSK), Trizivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 2000.[353]
- World sales of originator product: 2008: US$ 350 million; 2007: US$ 455 million; 2006: US$ 529 million; 2005: US$ 598 million; 2004: US$ 635 million.[354,355,356,357,358]
- Most patents on zidovudine (AZT), lamivudine (3TC), AZT/3TCa or abacavir (ABC) also affect this combination. In addition, GSK applied for patents more specifically related to the combination.[359]

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

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

	Daily dose	GSK	Aurobindo	Cipla	Matrix	Ranbaxy
Eligibility restrictions		see annex 2	None	None	None	None
AZT/3TC/ABC 300/150/300mg tablet (FDC)	2	**653 (0.895)**		414 (0.567)	365 (0.500)	**639 (0.875)**
AZT/3TC + ABC 300/150 + 300mg tablets (co-pack)	1 kit (4 tabs)		**402 (1.100)**			
AZT/3TC/ABC 60/30/60mg tablet (FDC)	4				**244 (0.167)**	

Products included in the WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there was one generic source of AZT/3TC/ABC 300/150/300mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is 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 three times what the most commonly used fixed-dose combination (3TC/d4T/NVP) costs today. This is predominately because of the high cost of abacavir (ABC).

Patents GlaxoSmithKline (GSK) could not apply for basic patents related to abacavir (ABC), zidovudine (AZT) or lamivudine (3TC) in some developing countries such as India, which did not grant patents on pharmaceuticals at the time. This allowed Indian generic companies to develop generic versions of each medicine, and of the combination. However, GSK widely applied for patents in other developing countries, where possible. In India, GSK had applied for patents more specifically related to the fixed-dose combination. The company withdrew the patent application after a pre-grant opposition was filed in 2006.[360]

Paediatrics The paediatric formulation of AZT/3TC/ABC is a generic version and is now listed on the WHO Prequalification List of Medicinal Products. However, this product is not commercially available yet because there is not enough market demand to make the product commercially viable.

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).[361,362]
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).[363]
- 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.[364]
- Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to nevirapine (NVP) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination, or for this specific FDC.

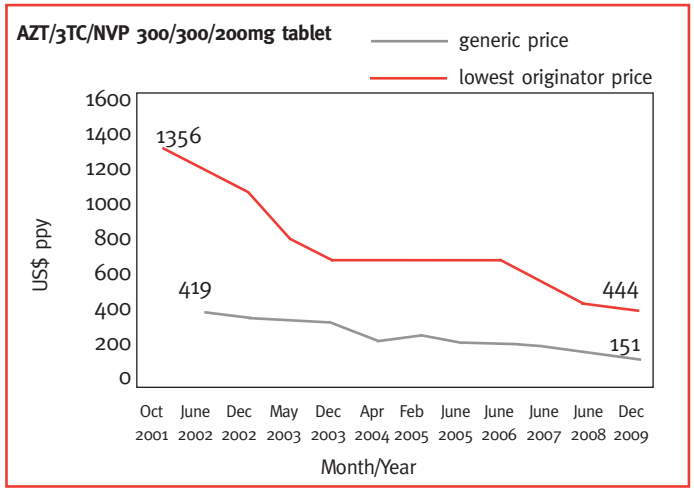
For information on the individual ARVs contained in this fixed-dose combination, please refer to the individual drug profiles.

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

	Daily dose	Aurobindo (CF)	Cipla (CF)	Matrix (CF)	Ranbaxy
Eligibility restrictions		None	None	None	None
AZT/3TC/NVP 300/150/200mg tablet	2	**158 (0.217)**	**151 (0.207)**	**158 (0.217)**	**183 (0.250)**
AZT/3TC/NVP 60/30/50mg tablet	4			**158 (0.108)**	

(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 WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.



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

As of December 2009, there were six generic sources of AZT/3TC/NVP 300/300/200mg listed on the WHO List of Prequalified Medicinal Products and the lowest-priced product on the List is shown here.

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

Generic prices have steadily decreased by 64% since 2001.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens.[375]

Patents In addition to the generic manufacturers referenced above, Apotex also manufactures an AZT/3TC/NVP fixed-dose combination[374] for export to developing countries under the 30 August 2003 World Trade Organization decision on compulsory licensing (CL) for export.[365]

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.[366]

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

Paediatrics The most-commonly used first-line regimens for children today are either AZT+3TC+NVP or d4T+3TC+NVP. Today, there is one paediatric AZT/3TC/NVP FDC tablet listed on the WHO List of Prequalified Medicinal Products.

For simplification, there is an urgent need for more sources of quality-assured triple FDCs, to allow children to be safely and accurately dosed.

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

General information

- Therapeutic class: two NRTI + one NNRTI in a co-blister.
- Indicated for first-line for adults, adolescents and children (WHO 2006 guidelines).[346,347]
- 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.[348]
- Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to efavirenz (EFV) also affect this combination. In addition, Cipla applied for patents specifically related to the use of AZT, 3TC and EFV in combination.[349]

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

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

	Daily dose	Aurobindo	Cipla	Ranbaxy	Strides
Eligibility restrictions		None	None	None	None
AZT/3TC + EFV 300/150 + 600mg tablets (co-pack)	1 kit (3 tabs)	**286 (0.783)**	320 (0.877)	**434 (1.190)**	**249 (0.682)**

Products included in the WHO List of Prequalified Medicinal Products (as of December 2009) are in **BOLD** in the table.

Spotlight on access issues:

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

In December 2009, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine-based regimens because of their long term irreversible side effects and to move towards zidovudine or tenofovir-based first-line regimens. Efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on TB treatment.[375]

Patents Basic patents related to zidovudine (AZT), lamivudine (3TC) or efavirenz (EFV) could not be obtained in some developing countries such as India, which did not grant product patents on pharmaceuticals at the time.

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

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

Annex 1: Summary 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**	**Matrix**	**Ranbaxy**	**Strides**		
300mg tablet	2	**261 (0.358)**	**237 (0.325)**	**437 (0.599)**	**243 (0.333)**	**341 (0.467)**			
20mg oral solution	10ml	**230 (0.063/ml)**	**204 (0.056/ml)**	**230 (0.063)**					
60mg tablet	4	**183 (0.125)**	134 (0.092)		**183 (0.125)**		730 (0.500)		
ATV		**BMS**		**Emcure**					
		Cat 1	Cat 2						
100mg capsule	3			**373 (0.341)**					
150mg capsule	2	**353 (0.484)**	**431 (0.590)**	**318 (0.435)**					
200mg capsule	--	(0.602)	(0.743)	**378 (0.518)**					
ddl		**Aurobindo**	**BMS**		**Cipla**	**Ranbaxy**			
			Cat 1	Cat 2					
25mg tablet	5		**212 (0.116)**	**433 (0.237)**	115 (0.063)	228 (0.125)			
50mg tablet	--		**(0.158)**	**(0.237)**	(0.079)	(0.115)			
100mg tablet	4	**207 (0.142)**	**310 (0.212)**	**366 (0.251)**	188 (0.129)	242 (0.166)			
150mg tablet	--	**(0.225)**	**(0.308)**	**(0.348)**	(0.167)				
200mg tablet	--	**(0.283)**	**(0.425)**		(0.257)				
125mg EC capsule	--	**(0.186)**							
200mg EC capsule	--	**(0.224)**							
250mg EC capsule	1	**172 (0.471)**	**223 (0.611)**	**249 (0.683)**	103 (0.283)				
400mg EC capsule	1	**270 (0.740)**	**288 (0.789)**	**322 (0.881)**	132 (0.363)				
2g powder for reconstitution	12ml	**88 (4.000/2g)**	**276(12.590/2g)**	**308(14.057/2g)**					
DRV		**Tibotec**							
300mg tablet	4	1095(0.750)							
EFV		**Aurobindo**	**Cipla**	**Emcure**	**Matrix**	**Merck**		**Ranbaxy**	**Strides**
						Cat 1	Cat 2		
50mg capsule	--	**(0.087)**				**(0.120)**	**(0.210)**		
50mg tablet	--					**(0.120)**	**(0.210)**		
100mg capsule	--	(0.150)							
200mg capsule	3	**152 (0.139)**	**146 (0.133)**			**394 (0.360)**	**821 (0.750)**	**171 (0.156)**	
200mg tablet	3					**394 (0.360)**	**821 (0.750)**		**128 (0.117)**
600mg tablet	1	**97 (0.267)**	**107 (0.292)**	**97 (0.267)**	**107 (0.292)**	**237 (0.650)**	**657 (1.800)**	**145 (0.397)**	**103 (0.281)**
30mg/ml suspension	--					**(0.094/ml)**	**(0.151/ml)**		

FPV	Daily dose	GSK								
700mg tablet	2	1222 (1.674)								
50mg/ml suspension	12ml	648 (0.148/ml)								
FTC		**Aurobindo**	**Matrix**							
200mg capsule	1	**67 (0.183)**	**79 (0.217)**							
IDV		**Aurobindo**	**Cipla**	**Merck**		**Ranbaxy**				
				Cat 1	Cat 2					
400mg capsule	4	365 (0.250)	422 (0.289)	**394 (0.270)**	**686 (0.470)**	426 (0.292)				
3TC		**Aurobindo**	**Cipla**	**GSK**	**Matrix**	**Ranbaxy**	**Strides**			
150mg tablet	2	**39 (0.053)**	**35 (0.048)**	**64 (0.087)**	**34 (0.046)**	**39 (0.054)**	**37 (0.050)**			
300mg tablet	1	**24 (0.067)**	41 (0.113)		**34 (0.092)**					
10mg/ml suspension	10ml	**29 (0.008/ml)**	**37 (0.010/ml)**	**84 (0.023/ml)**						
NFV		**Cipla**	**Roche**							
			Cat 1	Cat 2						
250mg tablet	10	945 (0.259)	**1612 (0.442)**	**2501 (0.685)**						
50mg/g oral powder	24g		**2189 (0.250/g)**	**2533 (0.289/g)**						
NVP		**Aurobindo**	**Boehringer**		**Cipla**	**Emcure**	**Huahai**	**Matrix**	**Ranbaxy**	**Strides**
			Cat 1	Cat 2						
200mg tablet	2	**42 (0.058)**	**219 (0.300)**	**438 (0.600)**	**35 (0.048)**	**42 (0.058)**	**35 (0.048)**	**42 (0.058)**	**47 (0.065)**	**42 (0.057)**
10mg/ml suspension	20ml	**66 (0.009/ml)**	**380 (0.052/ml)**	**533 (0.073/ml)**	**73 (0.010/ml)**					
RAL		**Merck**								
		Cat 1								
400mg tablet	2	1113 (1.525)								
RTV		**Abbott**	**Cipla**	**Strides**						
100mg capsule	2	**83 (0.114)**	313 (0.429)	219 (0.300)						
80mg/ml oral solution	--	**(0.093/ml)**								
SQV		**Cipla**	**Roche**							
			Cat 1	Cat 2						
200mg hard-capsule	10	1621 (0.444)	**1249 (0.342)**	**2501 (0.685)**						
500mg tablet	4		**1146 (0.785)**	**2499 (1.712)**						
d4T		**Aurobindo**	**BMS**		**Cipla**	**Matrix**	**Ranbaxy**	**Strides**		
			Cat 1	Cat 2						
15mg capsule	--	**(0.029)**	**(0.082)**	**(0.093)**	(0.024)					
20mg capsule	--	**(0.030)**	**(0.089)**	**(0.093)**	(0.025)					
30mg capsule	2	**22 (0.030)**	**48 (0.066)**	**68 (0.093)**	26 (0.035)	**24 (0.033)**	**26 (0.035)**	**22 (0.050)**		
1mg powder for suspension	20ml	**66 (0.009/ml)**	**51 (0.007/ml)**	**58 (0.008/ml)**	**44 (0.006/ml)**					

TDF	Daily dose	Aurobindo	Cipla	Gilead		Matrix	Strides		
				Cat 1	Cat 2				
300mg tablet	1	**116 (0.317)**	**100 (0.275)**	**207 (0.567)**	**365 (1.000)**	**116 (0.317)**	149 (0.408)		
		Aurobindo	**Cipla**	**GSK**	**Matrix**	**Ranbaxy**			
300mg tablet	2	**110 (0.150)**	**97 (0.133)**	**161 (0.221)**	**97 (0.133)**	**99 (0.135)**			
100mg capsule	--	**(0.092)**	**(0.050)**	**(0.122)**					
250mg capsule	--			**(0.276)**					
10mg/ml suspension	20ml	**73 (0.010/ml)**	**80 (0.011/ml)**	**234 (0.032/ml)**					
ABC/3TC		**Aurobindo**	**Cipla**	**GSK**	**Matrix**				
600/300mg tablet	1	**157 (0.429)**	152 (0.417)	484 (1.326)					
60/30mg tablet	4	**194 (0.133)**			**244 (0.167)**				
3TC/d4T		**Aurobindo**	**Cipla**	**Matrix**	**Ranbaxy**	**Strides**			
150/30mg tablet	2	**53 (0.072)**	**50 (0.068)**	**49 (0.067)**	**55 (0.075)**	**46 (0.063)**			
30/6mg dispersible tablet	4		**47 (0.032)**						
60/12mg dispersible tablet	2		**40 (0.055)**						
LPV/r		**Abbott**		**Aurobindo**	**Cipla**	**Matrix**			
		Cat 1	Cat 2						
133/33mg soft-gel capsule	6	**500 (0.228)**	**1000 (0.457)**		1218 (0.556)				
200/50mg tablet (heat-stable)	4	**400 (0.307)**	**1000 (0.685)**	**511 (0.350)**	486 (0.353)	**486 (0.333)**			
80/20mg solution	4ml	**176 (0.121/ml)**	**400 (0.274/ml)**						
100/25mg tablet (heat-stable)	3	**165 (0.151)**	**376 (0.343)**	**329 (0.300)**		**228 (0.208)**			
TDF/FTC		**Aurobindo**	**Cipla**	**Gilead**		**Matrix**			
				Cat 1	Cat 2				
300/200mg tablet	1	**164 (0.450)**	152 (0.417)	**319 (0.875)**	**548 (1.500)**	**158 (0.433)**			
TDF/3TC		**Cipla**	**Matrix**						
300/300mg tablet	1	134 (0.367)	**134 (0.367)**						
AZT/3TC		**Aurobindo**	**Cipla**	**Emcure**	**GSK**	**Matrix**	**Ranbaxy**	**Strides**	
300/150mg tablet	2	**122 (0.167)**	**117 (0.160)**	**91 (0.125)**	**197 (0.270)**	**122 (0.167)**	**124 (0.170)**	**146 (0.200)**	
60/30mg tablet	4	**146 (0.100)**				**121 (0.083)**			
3Tc/d4T/NVP		**Aurobindo**	**Cipla**	**Emcure**	**Matrix**	**Ranbaxy**	**Strides**		
30/6/50mg dispersible tablet	4		**61 (0.042)**						
60/12/100mg dispersible tablet	2		**55 (0.076)**						
150/30/200mg tablet	2	**82 (0.113)**	**80 (0.110)**	**88 (0.121)**	**85 (0.117)**	**93 (0.128)**	**91 (0.125)**		
TDF/FTC/EFV		**Cipla**	**Matrix**	**BMS/Gilead/Merck**					
				Cat 1	Cat 2				
300/200/600mg tablet	1	268 (0.733)	268 (0.733)	**613 (1.680)**	**1033 (2.830)**				

TDF/3TC/EFV	Daily dose	Cipla	Matrix						
300/300/600mg tablet (FDC)	1		243 (0.667)						
300/300 + 600mg (Co-pack)	1 kit (2 tabs)	350 (0.959)							
AZT/3TC/ABC		**Aurobindo**	**Cipla**	**GSK**	**Matrix**	**Ranbaxy**			
300/150/300mg tablet (FDC)	2		414 (0.567)	**653 (0.895)**	365 (0.500)	**639 (0.875)**			
300/150 + 300mg (Co-pack)	1 kit (4 tabs)	**402 (1.100)**							
60/30/60mg tablet (FDC)	4				**244 (0.167)**				
AZT/3TC/NVP		**Aurobindo**	**Cipla**	**Matrix**	**Ranbaxy**				
300/150/200mg tablet	2	**158 (0.217)**	**151 (0.207)**	**158 (0.217)**	**183 (0.250)**				
60/30/50mg tablet	4			**158 (0.108)**					
3TC/d4T + EFV		**Cipla**	**Ranbaxy**	**Strides**					
150/30 + 600mg (Co-pack)	1 kit (3 tabs)	274 (0.751)	**345 (0.945)**	176 (0.483)					
AZT/3TC + EFV		**Aurobindo**	**Cipla**	**Ranbaxy**	**Strides**				
150/300 + 600mg (Co-pack)	1 kit (3 tabs)	**286 (0.783)**	320 (0.877)	**434 (1.190)**	**249 (0.683**				

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 programs fully funded by governments, UN systems organizations, 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	**Category 1 countries:** Sub-Saharan African countries (except southern African countries) plus countries classified as low-income by the World Bank (except Korea, Kyrgyzstan, Moldova and Uzbekistan). **Category 2 countries:** Southern African countries See annex 7 for more details. For other developing countries, prices are negotiated on a case-by-case basis with BMS local representatives.	Both private and public sector organisations that are able to provide effective, sustainable and medically-sound care and treatment of HIV/AIDS.	Category 1 countries are invoiced in US$. Category 2 countries are invoiced in South African Rand.	CIP incoterm.
Boehringer Ingelheim	**Category 1 countries:** All LDCs, all low income countries and all of Africa **Category 2 countries:** All middle-income countries not included in category 1	Governments, NGOs and other partners who can guarantee that the programme is run in a responsible manner.		CIF.
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 - Freight charges separately on actual.

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.
Huahai	No reported restrictions.	Governments, non-profit institutional providers of HIV care, NGOs, and other private and public organisations that are able to provide responsible, sustainable and medically sound care.	For final purchase, price will be further negotiated, considering the factors like changes in exchange rate.	FCA Shanghai.
Matrix	No reported restrictions except 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	Please refer to Annex 10 for the individual drug country eligibility.	Governments, international organisations, NGOs, private sector organisations (e.g. employers, hospitals and insurers).	Merck may under certain circumstances supply ARVs to patients through retail pharmacies.	CIP.
Ranbaxy	No reported restrictions, but higher prices were negotiated separately for 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	**Category 1 countries:** All countries in sub-Saharan Africa and all countries classified as Least Developed Countries by the United Nations. **Category 2 countries:** Low-income 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	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 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; 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; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vanuatu; Yemen; Zambia.

Annex 4: Human Development Index (HDI)

Source: United Nations Development Programme (UNDP)
http://hdr.undp.org/en/media/hdr_20072008_en_complete.pdf

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

Low human development:
Afghanistan, Angola; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Congo (Democratic Republic); Côte d'Ivoire; Eritrea; Ethiopia; Gambia; Guinea; Guinea-Bissau; Liberia; Malawi; Mali; Mozambique; Niger; Nigeria; Rwanda; Senegal; Sierra Leone; Tanzania; Timor-Leste; Togo; Zambia.

Medium human development:
Algeria; Angola; Armenia; Azerbaijan; Bangladesh; Belize; Bhutan; Bolivia; Botswana; Cambodia; Cameroon; Cape Verde; China; Comoros; Congo; Djibouti; Dominican Republic; Egypt; El Salvador; Equatorial Guinea; Fiji; Gabon; Georgia; Ghana; Guatemala; Guyana; Haiti; Honduras; India; Indonesia; Iran; Jamaica; Jordan; Kenya; Kyrgyzstan; Lao PDR; Lesotho; Madagascar; Maldives; Mauritania; Moldova; Mongolia; Morocco; Myanmar; Namibia; Nepal; Nicaragua; Nigeria; Pakistan; Occupied Palestinian Territories; Papua New Guinea; Paraguay; Philippines; St. Vincent and the Grenadines; Samoa; São Tomé and Principe; Solomon Islands; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syrian Arab Republic; Tanzania; Tajikistan; Thailand; Tonga; Tunisia; Turkmenistan; Uganda; Ukraine; Uzbekistan; Vanuatu; Viet Nam; Yemen.

Annex 5: Sub-Saharan countries

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

Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius; Mayotte; Mozambique; Namibia; Niger; Nigeria; Rwanda; São Tomé and 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 updated every year on 1st July. This version is effective from 1st July 2009.

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; 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

1st Category 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.

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

Annex 8: Abbott eligible countries

Source: Abbott's Access to HIV Care Program

1st Category Countries: Africa and Least developed countries
Afghanistan; Algeria; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo-Brazzaville; Côte d'Ivoire; 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.

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

1st Category Countries: Low-Income Pricing Tier
Afghanistan; Algeria; Angola; Anguilla; Antigua and Barbuda; Bahamas; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; British Virgin Islands; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo, 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, U. Rep. of; Timor-Leste; Togo; Trinidad and Tobago; Tunisia; Turks and Caicos; Tuvalu; Uganda; Ukraine; Uzbekistan; Vanuatu; Vietnam; Yemen; Zambia; Zimbabwe.

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

Annex 10: Merck eligible countries

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

Merck's Pricing Policy for efavirenz and indinavir

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

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

NOTES:
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.
* In Botswana, Merck provides indinavir and efavirenz free of charge.
** Due to a special partnership in Romania, Merck provides indinavir and efavirenz at a 'no-profit price'.
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: Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

Merck's Pricing Policy for raltegravir
1st Category Countries:
Afghanistan; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo;

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

2nd Category Countries:
Algeria; Armenia; Azerbaijan; Belize; Bolivia; Brazil**; China; Colombia; Dominica; Dominican Rep.; Ecuador; Egypt; El Salvador; Fiji; Georgia; Grenada; Guatemala; Guyana; Honduras; India; Indonesia; Iran; Jamaica; Jordan; Kazakhstan; Kyrgyzstan; Lebanon; Moldova; Mongolia; Morocco; Nicaragua; Pakistan; Palestinian Territories; Peru; Philippines; St. Lucia; St. Vincent and the Grenadines; Sri Lanka; Suriname; Syria; Tajikistan; Thailand; Tunisia; Turkey; Turkmenistan; Ukraine; Uzbekistan; Venezuela; Viet Nam.

NOTES:
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. 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 provides raltegravir free of charge.
** Merck notes that Brazil "receives significant reduced pricing due to extraordinary commitment in treating HIV/AIDS patients."

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: Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

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

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

2nd Category Countries:
Bolivia; Indonesia; Kyrgyzstan; Mauritius; Mongolia; Nicaragua; Seychelles; Syria; Tajikistan; Uzbekistan; Viet Nam.

NOTES:
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.
* In Botswana, Merck provides TDF/FTC/EFV free of charge.
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: Iraq, Marshall Islands, Micronesia, Montenegro, Nauru, North Korea (DPR) and Palau.

Annex 11: Suggested resources for further information:

For documentation on prices quoted by companies:

• Back issues of Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries, can be found at: www.msfaccess.org

• 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

• Global HIV/Aids Epidemic Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited, January 2005: http://pdf.dec.org/pdf_docs/Pcaab266.pdf

For documentation on prices reported by countries:

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

• The Global Fund Price Reporting Mechanism
http://www.theglobalfund.org/en/funds_raised/price_reporting/default.asp

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

• WHO AFRO region Essential Medicines Price Indicator
http://www.who.int/medicines/publications/afro-essential_med_price_indicator_nocover.pdf

For documentation on patents:

• "Determining the patent status of essential medicines in developing countries", Health 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, DC, 2004
http://siteresources.worldbank.org/INTPROCUREMENT/Resources/Technical-Guide-HIV-AIDS.pdf

• "Drug patents under the spotlight. Sharing practical knowledge about pharmaceutical patents" MSF, June 2004. http://www.who.int/3by5/en/patents_2003.pdf

• Knowledge Ecology International http://www.keionline.org, or http://www.cptech.org/ip/health/

For documentation on quality:

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

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

Other useful websites referenced in this document:

• International Dispensary Association (IDA) Price Indicator
http://www.idafoundation.org/documents/ida_hiv_aids_aug_07_zondersnijlijnen.pdf

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

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

• WHO Registration http://ftp.who.int/htm/AMDS/drugsdatabase.pdf

• WHO Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

• Antiretroviral Therapy for HIV Infection in Infants and Children:Towards Universal Access: Recommendations for a public health approach 2007.
http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf

• UNICEF Procurement of HIV/AIDS Related Supplies. September 2007
http://www.unicef.org/supply/files/Procurement_of_HA_supplies(1).pdf

• Biotechnology/Pharmaceuticals HIV/AIDS Industry Report - April 2005
http://www.aethlonmedical.com/pdfs/IndustryReport.pdf

• Clinton Foundation Antiretroviral Price List
http://www.clintonfoundation.org/pdf/chai-arv-price-list-050807.pdf

• Access Campaign web site http://www.msfaccess.org

utw.msfaccess.org

We're delighted to announce the launch of an online version of Untangling the Web of Antiretroviral Price Reductions, Médecins Sans Frontières' guide to the prices of AIDS medicines, now in its 12th edition.

The online version reproduces the features of Untangling the Web - an analysis of the access to antiretrovirals environment, individual drug profile pages with prices quoted by companies, charts representing the evolution in price in previous years, and a spotlight on access issues including a look at patents and paediatrics - in a clear, user-friendly and free-flowing design.

Annex 12: Company contacts

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

TERMS & CONDITIONS

Prices listed below are available to countries participating in the CHAI Procurement Consortium, which currently includes over 70 nations. These prices apply to procurements by national governments that are members of the CHAI Procurement Consortium, or organizations procuring on behalf of member governments, to support public care and treatment programs. Products should be purchased directly from partner suppliers or through procurement agents representing the aforementioned programs. For TDF products offered by suppliers under a voluntary license from Gilead, indicated pricing is available only to countries covered under the voluntary license. Please contact Neeraj Mohan at nmohan@clintonfoundation.org with any questions related to this issue. Access to CHAI prices assumes prompt payment following the shipment of orders. Purchasers issuing requests for price quotes and/or tenders to which CHAI partner suppliers are invited to respond should reference membership in the CHAI Procurement Consortium, but requests and tenders need not be restricted to CHAI partner suppliers.

PRICES

CHAI prices represent price ceilings at or below which the indicated suppliers must price their products when selling or communicating price quotes for the specified products to members of the CHAI Procurement Consortium. In establishing price ceilings, CHAI aims to offer the lowest available prices to Consortium members while ensuring that products are available from more than one partner supplier wherever possible. Prices listed below are FCA Airport from the point of export. Per person per year prices for pediatric formulations are determined based on the recommended daily dosing for a 10 kg child (unless a formulation is not recommended for a 10kg child, in which case the annual price is calculated based on dosing for an applicable weight band). Note, in the April 2008 CHAI price list, per person per year pricing for five formulations – ABC 60mg, ABC+3TC 60/30mg, AZT+3TC 60/30mg, AZT+3TC+NVP 60/30/50mg and d4T 15mg – was calculated based on daily dosing for a pediatric weight band below 10 kg. Per person per year prices for these five formulations have been adjusted to reflect the annual cost of treatment for a 10kg 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), U.S. FDA or a stringent regulatory authority (SRA) as defined by the International Conference on Harmonization (ICH). In the list below, footnotes specify the applicable quality assurance status for each formulation: (1) Approved by the WHO Prequalification Programme; (2) Approved by the U.S. FDA or other SRA; (3) Recommended by the WHO Expert Review Panel; and (4) Submitted to the WHO, U.S. FDA or other SRA for review.

Clinton Foundation HIV/AIDS Initiative—Antiretroviral (ARV) Price List

ADULT PRODUCT		CEILING PRICE (USD)			SUPPLIER							
Name and strength	Packaging	Per year	Per pack	Per unit	Aurobindo	Cipla	Hetero	Hualuai	Macleods	Matrix	Ranbaxy	Strides
3TC (150mg)	HDPE bottle 60 tablets	$34	$2.83	$0.047	✓1,2	✓1	✓1,2		✓2	✓1,2	✓1,2	✓1,2
ABC (300mg)	HDPE bottle 60 tablets	$234	$19.50	$0.325	✓2	✓1,2				✓1,2		✓4
AZT (300mg)	HDPE bottle 60 tablets	$96	$8.00	$0.133	✓1,2	✓1	✓2			✓1,2	✓1,2	
AZT (300mg) + 3TC (150mg)	HDPE bottle 60 tablets	$115	$9.58	$0.160	✓1,2	✓1,2	✓1,2			✓1,2		✓1
AZT (300mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	$149	$12.42	$0.207	✓2	✓1,2	✓1			✓1,2		✓4
ATV (300mg)*	HDPE bottle 30 capsules	$265	$22.08	$0.736						✓4		
d4T (30mg)	HDPE bottle 60 capsules	$25	$2.08	$0.035	✓1,2		✓2		✓4	✓1,2	✓1	✓1,2
d4T (30mg) + 3TC (150mg)	HDPE bottle 60 tablets	$49	$4.08	$0.068	✓4	✓1,2				✓1,2		✓1,2
d4T (30mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	$89	$7.42	$0.124	✓3	✓1,2	✓1			✓1		✓2
ddI (100mg)	HDPE bottle 60 tablets	$185	$15.71	$0.128	✓2							
ddI (200mg)	HDPE bottle 60 tablets	$185	$15.42	$0.257	✓2							
ddI EC (250mg)	HDPE bottle 30 capsules	$156	$13.00	$0.433	✓2					✓4		
ddI EC (400mg)	HDPE bottle 30 capsules	$240	$20.00	$0.667	✓2					✓4		
DRV (600mg)	HDPE bottle 30 tablets	$303	$8.75	$0.292	✓1,2	✓1,2	✓1,2			✓1,2	✓1	✓1,2
LPV/r (200/50mg)	HDPE bottle 120 tablets	$470	$39.17	$0.326	✓2	✓3				✓1,2		
NVP (200mg)	HDPE bottle 60 tablets	$40	$3.33	$0.056	✓1,2	✓1,2	✓1,2	✓2	✓2	✓1,2	✓1,2	✓1,2
RTV (100mg), heat-stable*	HDPE bottle 30 tablets	$90	$7.50	$0.250						✓4		
TDF (300mg)	HDPE bottle 30 tablets	$99	$8.25	$0.275		✓1,2	✓4			✓2		✓4
TDF + 3TC (300/300mg)*	HDPE bottle 30 tablets	$120	$10.00	$0.333			✓4			✓2		
TDF + 3TC + EFV (300/300/600mg)	HDPE bottle 30 tablets	$210	$17.50	$0.583						✓4		
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	$150	$12.50	$0.417	✓2	✓4				✓2		✓4
TDF + FTC + EFV (300/200/600mg)	HDPE bottle 30 tablets	$239	$19.92	$0.664						✓3		

* CHAI has negotiated a price of USD $425 per person per year for a co-packaged once-daily second-line regimen containing ATV, heat-stable RTV and a fixed dose combination of TDF+3TC. This product will be available for procurement in 2010.

Clinton Foundation HIV/AIDS Initiative—Antiretroviral (ARV) Price List

PEDIATRIC PRODUCT		CEILING PRICE (USD)			SUPPLIER					
Name and strength	Packaging	Per year	Per pack	Per unit	Aurobindo	Cipla	Hetero	Macleods	Matrix	Strides
3TC (50mg/5ml)	HDPE bottle 240ml	$27	$1.80	$0.008	✓2	✓1,2				
ABC (20mg/ml)	HDPE bottle 240ml	$203	$13.53	$0.056	✓2	✓3				
ABC 60mg	HDPE bottle 60 tablets	$132	$5.50	$0.092	✓2				✓3	
ABC (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	$180	$7.50	$0.125	✓2				✓3	
AZT (50mg/5ml)	HDPE bottle 240ml	$64	$2.14	$0.009	✓2	✓1,2				
AZT (100mg)	HDPE bottle 100 capsules	$36	$5.00	$0.050	✓2	✓1,2			✓4	
AZT (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	$80	$3.33	$0.056	✓2,3				✓1	
AZT (60mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	$108	$4.50	$0.075					✓3	
d4T (1mg/ml)	HDPE bottle 200ml	$48	$1.34	$0.007	✓1,2	✓2				
d4T (15mg)	HDPE bottle 60 capsules	$17	$1.42	$0.024	✓2		✓2	✓4	✓2	
d4T (20mg)	HDPE bottle 60 capsules	$9	$1.50	$0.025	✓2		✓2	✓4	✓2	
d4T (6mg) + 3TC (30mg)	HDPE bottle 60 tablets	$48	$2.00	$0.033		✓2				
d4T (12mg) + 3TC (60mg)	HDPE bottle 60 tablets	$41	$3.42	$0.057		✓2				
d4T (6mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	$60	$2.49	$0.042		✓1,2				
d4T (12mg) + 3TC (60mg) + NVP (100mg)	HDPE bottle 60 tablets	$54	$4.54	$0.076		✓1,2				
ddI EC (125mg)	HDPE bottle 30 tablets	$67	$5.58	$0.186	✓2				✓4	
ddI EC (200mg)	HDPE bottle 30 tablets	$81	$6.75	$0.225	✓2				✓4	
EFV (50mg)	HDPE bottle 30 tablets	$27	$2.25	$0.075	✓2				✓4	
EFV (200mg)	HDPE bottle 90 capsules	$48	$12.00	$0.133	✓2	✓2			✓4	✓1
LPV/r (100/25mg)	HDPE bottle 120 tablets	$280	$23.33	$0.194	✓2				✓1	
NVP (50mg/5ml)	HDPE bottle 240ml	$55	$1.83	$0.008	✓1,2	✓1				

References

Note: As this document is based on the online version of Untangling the Web, references may appear more than once.

1.Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector, WHO, UNICEF, UNAIDS September 2009. http://data.unaids.org/pub/Report/2009/ 20090930_tuapr_2009_en.pdf

2. WHO HIV/AIDS data and statistics. 2008. Coverage and need for antiretroviral treatment (ART): Estimated number of people receiving ART, needing ART and percentage coverage in low- and middle-income countries according to region (December), http://www.who.int/hiv/data/coverage2008/en/index.html

3. Punishing Success? Early Signs of an International Retreat from Commitment to HIV/AIDS Care and Treatment. MSF Campaign for Access to Essential Medicines. Geneva. November 2009. http://www.msfaccess.org/fileadmin/user_upload/diseases/hiv-aids/11-16-REPORT_PunishingSuccess_A4_FINAL.pdf

4. The Treatment Timebomb - Report of the Enquiry of the All Party Parliamentary Group on AIDS into long-term access to HIV medicines in the developing world. July 2009.

5. The Treatment Timebomb - Report of the Enquiry of the All Party Parliamentary Group on AIDS into long-term access to HIV medicines in the developing world. July 2009.

6. The Antiretroviral Therapy Cohort Collaboration. 2008. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. The Lancet, 372, no. 9635 (July 26): 293-299, http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)61113-7/fulltext

7. Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector, WHO, UNICEF, UNAIDS September 2009. http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf, pg 72.

8. Nguyen et al, HIV Med, 2008

9. Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach, 2006 revision, WHO, Geneva (http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf)

10. Rosen S, Long L, Fox M, Sanne I. Cost and cost-effectiveness of switching from stavudine to tenofovir in first-line antiretroviral regimens in South Africa. Acquired Immune Deficiency Syndrome. 2008 Jul 1;48(3):334-44

11. Médecins Sans Frontières: HIV/AIDS treatment in developing countries: the battle for long-term survival has just begun. July 2009. www.msfaccess.org/resources/key-publications/key-publication-detail/?tx_ttnews[tt_news]=1580&cHash=f050be97d3

12. Khoo, s. et al. (2005) The potential for interactions between antimalarial and antiretroviral drugs. AIDS 19, 995-1005

13. http://www.who.int/malaria/malariandhivaids.html

14. FDA Modernization Act of 1997 - http://www.fda.gov/cder/guidance/105-115.html

15. Regulation (EC) No. 1901/2006 of the European Parliament and of the council of 12 December 2006 on medicinal products for pediatric use and amending Regulation(EEC) No. 1768/92, Director 2001/20/EC and Regulation (EC) NO. 726/2004 http://ec.europa.eu/enterprise/pharmaceuticals/eudrales/vol1/reg_2006_1901/reg_2006_1901_en.pdf

16. Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector, WHO, UNICEF, UNAIDS September 2009. http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf

17. Arendt V, Ndimubanzi P, Vyankandondera J, et al. AMATA study: effectiveness of antiretroviral therapy in breastfeeding mothers to prevent post-natal vertical transmission in Rwanda. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract TUAX102

18. Guidelines for use of Antiretroviral agents in Paediatric HIV infection Feb 28, 2008, Supplementary 1 Drug Information. http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf

19. The Treatment Timebomb - Report of the Enquiry of the All Party Parliamentary Group on AIDS into long-term access to HIV medicines in the developing world. July 2009.

20. http://www.msfaccess.org/main/access-patents/introduction-to-access-and-patents/milestones/2007-save-the-pharmacy-of-the-developing-world/

21. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

22. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf

23. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

24. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html

25. GlaxoSmithKline Annual Report 2004. http://www.gsk.com/investors/annual-reports-04.htm

26. GlaxoSmithKline Annual Report 2005. http://www.gsk.com/investors/annual-reports-05.htm

27. GlaxoSmithKline Annual Report 2006. http://www.gsk.com/investors/repso6/annual-report-2006.pdf

28. GlaxoSmithKline Annual Report 2007. http://www.gsk.com/investors/repso7/annual-report-2007.pdf

29. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/repso8/GSK-Report-2008-full.pdf

30. European Patent Office: Therapeutic nucleosides. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0349242&F=0

31. European Patent Office: Therapeutic nucleosides. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0434450&F=0

32. European Patent Office: Carbocyclic nucleoside hemisulfate and its use in treating viral infections. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9852949&F=8&QPN=WO9852949

33. European Patent Office: Pharmaceutical compositions. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9939691&F=0&QPN=WO9939691

34. Initiative for Medicines, Access and Knowledge, Abacavir Sulfate. http://www.i-mak.org/abacavir-sulfate/

35. http://210.210.88.164/patentgrantedSearch/displayApplication.asp?application_number=IN/PCT/2000/193/KOL

36. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

37. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf

38. Pharmaceutical Benefit Scheme Australia http://www.pbs.gov.au/html/healthpro/home (accessed 22.9.09).

39. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

40. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

41. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

42. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html

43. GlaxoSmithKline Annual Report 2005. http://www.gsk.com/investors/annual-reports-05.htm

44. GlaxoSmithKline Annual Report 2006. http://www.gsk.com/investors/repso6/annual-report-2006.pdf

45. GlaxoSmithKline Annual Report 2007. http://www.gsk.com/investors/repso7/annual-report-2007.pdf

46. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/repso8/GSK-Report-2008-full.pdf

47. European Patent Office: Synergistic combinations of zidovudine, 1592U89 and 3TC or FTC http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9630025&F=1&QPN=WO9630025

48. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/repso8/GSK-Report-2008-full.pdf

49. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html

50. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public health approach 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

51. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

52. Unedited draft report on the 17th expert committee on the selection and use of essential medicines, 2009, World Health Organization, Geneva. http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf

53. Bristol-Myers Squibb Annual Report 2008. http://library.corporate-ir.net/library/10/106/106664/items/329615/89F48B26-8E28-4566-8F26-AA9133B83124_BMS_AR08.pdf

54. Bristol-Myers Squibb Annual Report 2007. http://www.bmsa.com.au/documents/2007annualreport.pdf
55. Bristol-Myers Squibb Press Release: Bristol Myers Squibb Company Reports Financial Results for the 4th Quarter and 12 Months of 2006 and Announces EPS Guidance for 2007. 25 January 2007. http://www.bms.com/news/press_releases/pages/default.aspx
56. "Will once-daily Kaletra be enough to see off the threat of Reyataz?" Pharmaceutical Business Review, 20 May 2005. http://www.hospitalpharma.com/features/feature.asp?ROW_ID=591
57. European Patent Office: Antivirally Active Heterocyclic Azahexane Derivatives. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9740029&F=8&QPN=WO9740029
58. European Patent Office: Antivirally Active Heterocyclic Azahexane Derivatives. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9936404&F=8&QPN=WO9936404
59. European Patent Office: Process For Preparing Atazanavir Bisulfate And Novel Forms. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO2005108349&F=8&QPN=WO2005108349
60. Patent Opposition. Lawyers Collective: The Third Eye of the Law. http://www.lawyerscollective.org/amtc/patent-opposition
61: BMS Economic Performance http://www.bms.com/static/ehs/report/data/eco_06.pdf
62. Recomendações para Terapia, Anti-retroviral em Adultos, Infectados pelo HIV, 2008. http://www.aids.gov.br/data/documents/storedDocuments/%7BB8EF5DAF-23AE-4891-AD36-1903553A3174%7D/%7B762E0EBF-A859-4779-8A92-704EB1F3B290%7D/consensoAdulto005c_2008montado.pdf
63. Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group Meeting, 2008, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf
64. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
65. Product Information: PREZISTA oral tablets, Darunavir oral tablets. Tibotec Therapeutics, Division of Ortho Biotech Products, Raritan, NJ, 2006
66. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
67. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
68. European Patent Office: Hydroxyethylamino Sulfonamides Useful As Retroviral Protease Inhibitors. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9404492&F=1&QPN=WO9404492
69. European Patent Office: Multi-Drug Resistant Retroviral Protease Inhibitors And Associated Methods. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9967254&F=0&QPN=WO9967254
70. http://scientific.thomsonreuters.com/gazettenews/2007/25.pdf - link no longer works
71. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=WO03049746&F=0
72. European Patent Office: Combination Of Cytochome P›450‹ Dependent Protease Inhibitors. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO03106461&F=1&QPN=WO03106461
73. http://www.tibotec.com/news/detail.jhtml?itemname=news_31
74. Pharmaceutical Benefit Scheme Australia http://www.pbs.gov.au/html/healthpro/home (accessed 14.11.2009)
75. Antiretroviral Therapy of HIV infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
76. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
77. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
78. Bristol-Myers Squibb Annual Report 2005. http://library.corporate-ir.net/library/10/106/106664/items/189260/BMY_AR_05.pdf
79. Pharmaceutical Benefit Scheme Australia http://www.pbs.gov.au/html/healthpro/home (accessed 28.8.09).
80. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public health approach 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
81. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
82. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
83. Bristol-Myers Squibb company worldwide net sales from continuing operations by product quarterly sales trend analysis. http://www.bms.com/irdocs/product_sales_1q08.pdf
84. Bristol-Myers Squibb company reports Financial results for the 4th quarter and 12 months of 2006 and announces EPS guidance for 2007 http://www.bms.com/irdocs/4q06earn.pdf
85. Bristol-Myers Squibb Annual Report 2005. http://library.corporate-ir.net/library/10/106/106664/items/189260/BMY_AR_05.pdf
86. Bristol-Myers Squibb Annual Report 2008. http://library.corporate-ir.net/library/10/106/106664/items/329615/89F48B26-8E28-4566-8F26-AA9133B83124_BMS_AR08.pdf
87. European Patent Office: Benzoxazinones As Inhibitors Of HIV Reverse Transcriptase. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=CA2101572&F=0&RPN=WO9403440&DOC=deb45b02a96924db95500bc28a42e9b960
88. Facts and Evidences on the 10 Burning Issues Related to the Government Use of Patents on Three Patented Essential Drugs in Thailand. Ministry of Public Health and National Health Security Office, Thailand, 2007. http://www.moph.go.th/hot/White%20Paper%20CL-EN.pdf
89. Personal communication with Kannikar Kijtiwatchakul, price quoted in Thai Baht converted to US$ through www.oanda.com (accessed 21.09.2009).
90. Brazilian Ministry of Health Press Release: Brazilian Government declares efavirenz to be of public interest. 25 April 2007. http://www.aids.gov.br/main.asp?View={E77B47C8-3436-41E0-AC19-E1B215447EB9}&BrowserType=IE&LangID=en&params=itemID={D3ED04F7-1D8D-4681-9F52-E948F99783B3};&UIPartUID={D90F22DB-05D4-4644-A8F2-FAD4803C8898}
91. Treatment Action Campaign Press Release: TAC complaint increases access to efavirenz: MSD finally agrees to grant licenses on reasonable terms. 1 June 2008. http://www.tac.org.za/community/node/2329
92. European Patent Office: Crystalline Efavirenz http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9964405&F=8&QPN=WO9964405
93. Patent Opposition. Lawyers Collective: The Third Eye of the Law. http://www.lawyerscollective.org/amtc/patent-opposition
94. World Intellectual Property Organization: (WO/2004/064845) Compositions And Methods For Combination Antiviral Therapy. http://www.wipo.int/pctdb/en/wo.jsp?wo=2004064845
95. World Intellectual Property Organzation: (WO/2006/135933) Stable Fixed-Dose Unitary Formulations Containing Tenofovir, A Surfactant, Efavirenz And Emtricitabine. http://www.wipo.int/pctdb/en/wo.jsp?wo=2006135933
96. http://www.gnaipr.com/CaseLaws/3383DELNP2005%20-%20Decision.pdf
97. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
98. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
99. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
100. From 10-K Gilead Sciences, 2007. http://www.gilead.com/pdf/GILEADSCIENCESI10K.pdf
101. Gilead Sciences Press Release: Gilead sciences announces 4th quarter and full year 2007 financial results. 23 January 2008. http://www.gilead.com/pr_1099304
102. Gilead Sciences Press Release: Glilead Sciences announces 4th quarter and full year 2008 financial results. 27 January 2009. http://www.gilead.com/pr_1248887
103. European Patent Office: Substituted -1,3-oxathiolanes with antiviral properties. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0382526&F=0
104. http://scientific.thomsonreuters.com/media/cdjournals/gazettenews/2002/CPG_News_0224.pdf
105. European Patent Office: Method And Compositions For The Synthesis Of BCH-189 And Related Compounds. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9111186&F=0&QPN=WO9111186
106. European Patent Office: Antiviral Activity And Resolution Of 2-Hydroxymethyl-5-(5-Fluorocytosin-1-Yl)-1,3-Oxathiolane. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9214743&F=8&QPN=WO9214743
107. Gilead Sciences Press Release: Gilead Sciences and Royalty Pharma Announce $525 Million Agreement with Emory University to Purchase Royalty Interest for Emtricitabine. 18 July 2005. http://www.gilead.com/pr_731707
108. http://www.keionline.org/index.php?option=

com_content&task=view&id=23&Itemid=5
109. Gilead Sciences - Partnerships. http://www.gilead.com/access_partnerships
110. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
111. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
112. http://www.keionline.org/index.php?option=com_content&task=view&id=23&Itemid=5
113. Gilead Sciences - Partnerships. http://www.gilead.com/access_partnerships
114. Product Information: Fuzeon, enfuvirtide for injection. Roche Laboratories Inc. & Trimeris Inc. 2007
115. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
116. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html117. European Patent Office: Synthetic Peptide Inhibitors Of Hiv Transmission. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9428920&F=0&QPN=WO9428920
118. European Patent Office: Recombinant proteins of viruses associated with lymphadenopathy syndrome and/or acquired immune deficiency syndrome. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0181150&F=1&QPN=EP0181150&OREQ=0&
119. http://scientific.thomsonreuters.com/media/cdjournals/gazettenews/2006/CPG_News_0613.pdf
120. http://scientific.thomsonreuters.com/media/cdjournals/gazettenews/2006/CPG_News_0613.pdf
121. Pharmaceutical Benefit Scheme Australia. www.pbs.gov.au. Conversion to US$ www.oanda.com.
122. Product Information: INTELENCE oral tablets, etravirine oral tablets. Tibotec Therapeutics, Division of Ortho Biotech Products, Raritan, NJ, 2008
123. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
124. European Patent Office: Hiv Replication Inhibiting Pyrimidines. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO0027825&F=0&QPN=WO0027825
125. Janssen Pharmaceutica. http://www.janssenpharmaceutica.be/about_jp_E.asp
126. Tibotec. http://www.tibotec.com/bgdisplay.jhtml?itemname=about
127. http://210.210.88.164/patentgrantedSearch/displayApplication.asp?application_number=IN/PCT/2001/00436/MUM
128. European Medicines Agency decision of 27 January 2009 on the agreement of a Paediatric Investigation Plan and on granting of a deferral and on the granting of a waiver for etravirine, EMEA-000222-PIP01-08 in accordance with Regulation (EC) No 1091/2006 of the European Parliament and of the Council as amended. http://www.emea.europa.eu/pdfs/human/paediatrics/000222-PIP01-08.pdf
129. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
130. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
131. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
132. European Patent Office: Sulphonamide Derivatives As Prodrugs Of Aspartyl Protease Inhibitors. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9933815&F=1&QPN=WO9933815
133. Ouyang, Hui. Case Study: Fosamprenavir: A Prodrug of Amprenavir. SpringerLink, 2008. http://www.springerlink.com/content/po5m15485110301o/?p=0eb3f6f80327487a885192b60b204bb88&pi=8
134. OAPI: African Intellectual Property Organization. http://www.oapi.wipo.net/en/OAPI/historique.htm
135. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
136. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public health approach 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
137. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
138. Unedited draft report on the 17th expert committee on the selection and use of essential medicines, 2009, World Health Organization, Geneva. http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf
139. European Patent Office: HIV Protease Inhibitors Useful For The Treatment Of AIDS. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9309096&F=8&QPN=WO9309096
140. Merck & CO. Crixivan Product Information. http://www.merck.com/product/usa/pi_circulars/c/crixivan/crixivan_pi.pdf
141. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
142. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
143. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
144. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
145. GlaxoSmithKline Annual Report 2006. http://www.gsk.com/investors/repso6/annual-report-2006.pdf
146. GlaxoSmithKline Annual Report 2007. http://www.gsk.com/investors/repso7/annual-report-2007.pdf
147. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/repso8/GSK-Report-2008-full.pdf
148. European Patent Office: Substituted -1,3-oxathiolanes with antiviral properties. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0382526&F=0
149. http://scientific.thomsonreuters.com/media/cdjournals/gazettenews/2002/CPG_News_0224.pdf
150. European Patent Office: Crystalline oxathiolane derivatives. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=EP0517145&F=0&RPN=WO9221676&DOC=deb45b02a96922db93500ecb934bf2c269&QPN=WO9221676
151. European Patent Office: Pharmaceutical Compositions Containing Lamivudine http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_EP&FT=D&date=20010111&CC=IL&NR=131917A&KC=A
152. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
153. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
154. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a Public Health Approach, 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
155. Addendum To 2006 Who Guidelines on Antiretroviral Therapy For HIV Infection in Adults and Adolescents. http://www.who.int/hiv/art/ARTadultsaddendum.pdf
156. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
157. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
158. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public health approach 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
159. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
160. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
161. Addendum To 2006 Who Guidelines on Antiretroviral Therapy For HIV Infection in Adults and Adolescents. http://www.who.int/hiv/art/ARTadultsaddendum.pdf
162. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
163. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
164. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

165. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach, 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
166. Addendum to 2006 Who Guidelines on Antiretroviral Therapy For HIV Infection in Adults and Adolescents. http://www.who.int/hiv/art/ARTadultsaddendum.pdf
167. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
168. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
169. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
170. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
171. Addendum To 2006 Who Guidelines on Antiretroviral Therapy For HIV Infection in Adults and Adolescents. http://www.who.int/hiv/art/ARTadultsaddendum.pdf
172. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
173. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach, 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
174. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
175. Unedited draft report on the 17th expert committee on the selection and use of essential medicines, 2009, World Health Organization, Geneva. http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf
176. Abbott Laboratories Highlights from Recent Management Meetings, North America Equity Research, 6th July 2005
177. Abbott Reports 16.1 Percent Sales Growth in Fourth Quarter. Reuters, 23 January 2008. http://www.reuters.com/article/pressRelease/idUS134075+23-Jan-2008+PRN20080123
178. European Patent Office: Retroviral Protease Inhibiting Compounds. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9721685&F=0&QPN=WO9721685
179. European Patent Office: Pharmaceutical Composition. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9822106&F=1&QPN=WO9822106
180. European Patent Office: Solid Pharmaceutical Dosage Form. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO2005039551&F=0&QPN=WO2005039551
181. Initiative for Medicines, Access & Knowledge. Lopinavir/ritonavir. http://www.i-mak.org/lopinavirritonavir/
182. Facts and Evidences on the 10 Burning Issues Related to the Government Use of Patents on Three Patented Essential Drugs in Thailand. Ministry of Public Health and National Health Security Office, Thailand, 2007. http://www.moph.go.th/hot/White%20Paper%20CL-EN.pdf
183. Personal communication with Kannikar Kijtiwatchakul, MSF Thailand. Price quoted in Thai Baht converted to US$ through www.oanda.com (accessed 21.09.2009).
184. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
185. Product Information: Selzentry oral tablets, Maraviroc oral tablets. Pfizer, Inc., NY, 2007
186. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
187. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
188. European Patent Office: Azabicycloalkanes as CCR5 Modulators. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO0038680&F=1&QPN=WO0038680
189. European Patent Office: Tropane Derivatives Useful in Therapy. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO0190106&F=1&QPN=WO0190106
190. http://210.210.88.164/patentgrantedSearch/displayApplication.asp?application_number=IN/PCT/2002/00923/DEL
191. ARIPO: African Regional Intellectual Property Organisation. http://www.aripo.org/index.php?option=com_content&view=article&id=19&Itemid=53
192. OAPI : African Intellectual Property Organization. http://www.oapi.wipo.net/en/OAPI/historique.htm
193. 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. http://www.ncbi.nlm.nih.gov/pubmed/18598916?dopt=Abstract
194. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
195. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach, 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
196. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
197. Unedited draft report on the 17th expert committee on the selection and use of essential medicines, 2009, World Health Organization, Geneva. http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf
198. Major developments in the treatment of HIV/AIDS, Biotechnology/pharmaceuticals HIV/AIDS Industry Report, 2005. http://www.aethlonmedical.com/pdfs/IndustryReport.pdf
199. European Patent Office: HIV Protease Inhibitors. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9509843&F=1&QPN=WO9509843
200. Roche investor update: European licence for Roche HIV drug Viracept recommended for re-instatement, 20 September 2007. http://www.roche.com/inv-update-2007-09-20e
201. Prequalification Programmme, World Health Organization. http://mednet3.who.int/prequal/
202. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
203. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
204. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
205. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
206. Boehringer Ingelheim Annual Report 2007. http://www.boehringer-ingelheim.com/corporate/news/information_material/publication_download.asp
207. Boehringer Ingelheim Annual Report 2004.
208. Boehringer Ingelheim Annual Report 2005.
209. Boehringer Ingelheim Annual Report 2006. http://www.boehringer-ingelheim.com/corporate/download/ar/BI_AR2006_en.pdf
210. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0429987&F=8
211. European Patent Office: 5,11-Dihydro-6H-dipyrido[3,2-b:2',3'-e] [1,4]diazepines and their use in the prevention or treatment of HIV infection. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9909990&F=0&QPN=WO9909990
212. European Patent Office: Extended Release Formulation of Nevirapine. http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_V3&FT=D&date=20081218&CC=AU&NR=2008262031A1&KC=A1
213. Lawyers Collective. "Patent for Nevirapine Rejected". http://www.lawyerscollective.org/amtc/patent-opposition/nevirapine
214. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva.http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
215. Product Information: ISENTRESS oral tablets, raltegravir oral tablets. Merck & Co, Inc, Whitehouse Station, NJ, 2007.
216. Merck Form 10-K, 2008. http://media.corporate-ir.net/media_files/irol/73/73184/MRKForm10K2008final.pdf
217. European Patent Office: N-Substituted Hydroxypyrimidinone Carboxamide Inhibitors Of HIV Integrase. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO03035077&F=0&QPN=WO03035077
218. European Patent Office: Potassium Salt of an HIV Intergrase Inhibitor. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO2006060712&F=0&QPN=WO2006060712
219. Intellectual Property India, Office of Controller General of Patents Designs, and Trademarks, Indian Patent Information Retrieval System. http://124.124.220.66/patentpublishedsearch/(X(1)S(vwtbyg55rktpxj55b3p51u55))/publishApplicationNumber.aspx?application_number=868/CHENP/2004&AspxAutoDetectCookieSupport=1

220. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
221. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach, 2006, World Health Organization, Geneva.http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
222. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
223. Unedited draft report on the 17th expert committee on the selection and use of essential medicines, 2009, World Health Organization, Geneva. http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf
224. Abbott Laboratories Highlights from Recent Management Meetings, North America Equity Research, 6th July 2005
225. European Patent Office: Retroviral Protease Inhibiting Compounds. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9414436&F=1&QPN=WO9414436
226. European Patent Office: Pharmaceutical Composition. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9822106&F=1&QPN=WO9822106 or for new forms of RTV, such as the crystalline polymorph in 1999
227. European Patent Office: Polymorph of a Pharmaceutical. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO0004016&F=1&QPN=WO0004016.
228. Initiative for Medicines, Access & Knowledge. Lopinavir/ritonavir. http://www.i-mak.org/lopinavirritonavir/
229. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
230. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
231. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
232. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
233. European Patent Office: Amino acid derivatives. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0432695&F=1
234. European Patent Office: Saquinavir Mesylate Oral Dosage Form. http://v3.espacenet.com/publicationDetails/biblio?DB=EPODOC&adjacent=true&locale=en_V3&FT=D&date=20050120&CC=WO&NR=2005004836A2&KC=A2
235. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
236. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
237. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
238. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
239. WHO Model list of Essential Medicines, 15th list, March 2007, World Health Organization, Geneva. http://www.who.int/medicines/publications/EssMedList15.pdf
240. Bristol-Myers Squibb Company Reports First Quarter 2006 Financial Results . Bristol-Myers Squibb. http://investor.bms.com/phoenix.zhtml?c=106664&p=irol-newsArticle&ID=848516&highlight=
241. Bristol-Myers Squibb Annual Report 2005. http://library.corporate-ir.net/library/10/106/106664/items/189260/BMY_AR_05.pdf
242. Consumer Project on Technology. Stavudine (d4T). http://www.cptech.org/ip/health/d4T.html
243. European Patent Office: Pharmaceutical composition comprising 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) in treating patients infected with retrovirus. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=EP0273277&F=8
244. Consumer Project on Technology. Stavudine (d4T). http://www.cptech.org/ip/health/d4T.html
245. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
246. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
247. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
248. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
249. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
250. Gilead Sciences Form 10-K, 2007. http://www.gilead.com/pdf/GILEADSCIENCESI10K.pdf
251. Gilead Sciences Annual Report 2005. http://ccbn.mobular.net/ccbn/7/1377/1472/print/print.pdf
252. Gilead Sciences Annual Report 2006. http://www.gilead.com/AR2006/GILEAD%20AR06_final.pdf
253. Gilead Sciences Press Release: Gilead Sciences announces 4th quarter and full year 2007 financial results, 23 January 2008. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle&ID=1099304&highlight=
254. Gilead Sciences Press Release: Gilead Sciences announces 4th quarter and full year 2008 financial results, 27 January 2009. http://www.gilead.com/pr_1248887
255. European Patent Office: 9-(phosponylmethoxyalkyl) adenines, the method of preparation and utilization thereof. http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=US4808716&F=0&RPN=EP0206459&DOC=cca34af1984f08bf7c37f3b37b34dbab52&QPN=EP0206459
256. European Patent Office: Nucleotide Analogs. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9804569&F=8&QPN=WO9804569
257. European Patent Office: Nucleotide Analog Composition And Synthesis Method. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9905150&F=8&QPN=WO9905150
258. World Intellectual Property Organization: (Wo/2004/064845) Compositions And Methods For Combination Antiviral Therapy. http://www.wipo.int/pctdb/en/wo.jsp?wo=2004064845
259. World Intellectual Property Organization: (Wo/2006/135933) Stable Fixed-Dose Unitary Formulations Containing Tenofovir, A Surfactant, Efavirenz And Emtricitabine. http://www.wipo.int/pctdb/en/wo.jsp?wo=2006135933
260. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/896.DEL.2002_Intermed%20Labs.PDF
261. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/2076.DEL.1997_Cipla.PDF
262. http://www.gnaipr.com/CaseLaws/3383DELNP 2005%20-%20Decision.pdf
263. Gilead Sciences: Partnerships. http://www.gilead.com/access_partnerships
264. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
265. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
266. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
267. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
268. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
269. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
270. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html271. Gilead Sciences Press Release: Gilead Sciences announces 4th quarter and full year 2008 financial results, 27 January 2009. http://www.gilead.com/pr_1248887
272. World Intellectual Property Organization: (Wo/2004/064845) Compositions And Methods For Combination Antiviral Therapy. http://www.wipo.int/pctdb/en/wo.jsp?wo=2004064845
273. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/896.DEL.2002_Intermed%20Labs.PDF
274. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/2076.DEL.1997_Cipla.PDF
275. http://www.gnaipr.com/CaseLaws/3383DELNP2005

%20-%20Decision.pdf
276. Gilead Sciences: Partnerships. http://www.gilead.com/access_partnerships
277. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
278. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
279. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
280. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
281. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
282. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
283. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
284. Gilead Sciences Press Release: Gilead Sciences announces 4th quarter and full year 2008 financial results, 27 January 2009. http://www.gilead.com/pr_1248887
285. World Intellectual Property Organization: (Wo/2006/135933) Stable Fixed-Dose Unitary Formulations Containing Tenofovir, A Surfactant, Efavirenz And Emtricitabine. http://www.wipo.int/pctdb/en/wo.jsp?wo=2006135933
286. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
287. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/896.DEL.2002_Intermed%20Labs.PDF
288. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/2076.DEL.1997_Cipla.PDF
289. http://www.gnaipr.com/CaseLaws/3383DELNP2005%20-%20Decision.pdf
290. Gilead Sciences: Partnerships. http://www.gilead.com/access_partnerships
291. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
292. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
293. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
294. WHO Model list of Essential Medicines, 15th list, March 2007, World Health Organization, Geneva. http://www.who.int/medicines/publications/EssMedList15.pdf
295. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
296. European Patent Office: Pharmaceutical Combination. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO2007068934&F=0&QPN=WO2007068934
297. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/896.DEL.2002_Intermed%20Labs.PDF
298. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/2076.DEL.1997_Cipla.PDF
299. http://www.gnaipr.com/CaseLaws/3383DELNP2005%20-%20Decision.pdf
300. Gilead Sciences: Partnerships. http://www.gilead.com/access_partnerships
301. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
302. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
303. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
304. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
305. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
306. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
307. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/896.DEL.2002_Intermed%20Labs.PDF
308. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/storage/2076.DEL.1997_Cipla.PDF
309. http://www.gnaipr.com/CaseLaws/3383DELNP2005%20-%20Decision.pdf
310. Gilead Sciences: Partnerships. http://www.gilead.com/access_partnerships
311. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
312. Product Information: APTIVUS(R) oral capsules, tipranavir oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, 2007
313. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
314. European Patent Office: Pyranone Compounds Useful To Treat Retroviral Infections. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9530670&F=0&QPN=WO9530670
315. European Patent Office: Self-Emulsifying Formulation For Lipophilic Compounds. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9906043&QPN=WO9906043
316. European Patent Office: Pharmaceutical Composition For Acidic Lipophilic Compounds In A Form Of A Self-Emulsifying Formulation. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9906044&QPN=WO9906044
317. Agencia Nacional de Vigilancia Sanitaria, Brazil. See patent application no. PI 9507615-8 http://www.anvisa.gov.br/medicamentos/intelectual/situacao_processos.pdf
318. Cadernos Pela Vidda - Aids, Tratamento e Ativismo. Nº 44, Ano XVII, April 2007. Novos medicamentos: alternativas para a falência terapêutica (New Medicines: alternatives for therapeutic failure). Pages 4-7 http://www.aids.org.br/media/File/cadernos/CPV_n44.pdf
319. Newspaper Estado de São Paulo (19th January 2008) Empresa deixa de lançar antiaids por discordar de lei de patentes do País (Company refrains from launching and anti-AIDS drug because it disagrees with the patent law of the country) http://www.estado.com.br/editorias/2008/01/19/ger-1.93.7.20080119.1.1.xml
320. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
321. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
322. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
323. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
324. GlaxoSmithKline Annual Report 2004. http://www.gsk.com/investors/annual-reports-04.htm
325. GlaxoSmithKline Annual Report 2005. http://www.gsk.com/investors/annual-reports-05.htm
326. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
327. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
328. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
329. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/

artadultguidelines.pdf
330. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
331. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
332. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
333. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
334. GlaxoSmithKline Annual Report 2004. http://www.gsk.com/investors/annual-reports-04.htm
335. GlaxoSmithKline Annual Report 2005. http://www.gsk.com/investors/annual-reports-05.htm
336. GlaxoSmithKline Annual Report 2006. http://www.gsk.com/investors/reps06/annual-report-2006.pdf
337. GlaxoSmithKline Annual Report 2007. http://www.gsk.com/investors/reps07/annual-report-2007.pdf
338. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/reps08/GSK-Report-2008-full.pdf
339. European Patent Office: Antiviral Combinations Containing Nucleoside Analogs. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9220344&F=0&QPN=WO9220344
340. European Patent Office: Pharmaceutical Compositions Containing Lamivudine And Zidovudine. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9818477&F=0&QPN=WO9818477
341. Patent Opposition. Lawyers Collective: The Third Eye of the Law. http://www.lawyerscollective.org/amtc/patent-opposition
342. GlaxoSmithKline Press Release: GSK patents and patent applications for Combivir, 10 August 2006. http://www.gsk.com/media/pressreleases/2006/2006_08_10_GSK874.htm
343. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
344. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
345. Prioritizing Second Line Antiretroviral Drugs for Adults and Adolescents: A Public Health Approach, Report of a WHO Working Group Meeting, May 2007, Geneva. http://www.who.int/hiv/pub/meetingreports/Second_Line_Antiretroviral.pdf
346. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
347. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
348. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
349. European Patent Office: Pharmaceutical Combinations Comprising Lamivudine, Zidovudine And Efavirenz For Treating Viral Infections. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO2004089382&F=8&QPN=WO2004089382
350. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
351: Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
352. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
353. U.S. Food and Drug Administration: Drugs@FDA - FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
354. GlaxoSmithKline Annual Report 2004. http://www.gsk.com/investors/annual-reports-04.htm
355. GlaxoSmithKline Annual Report 2005. http://www.gsk.com/investors/annual-reports-05.htm
356. GlaxoSmithKline Annual Report 2006, http://www.gsk.com/investors/reps06/annual-report-2006.pdf
357. GlaxoSmithKline Annual Report 2007. http://www.gsk.com/investors/reps07/annual-report-2007.pdf
358. GlaxoSmithKline Annual Report 2008. http://www.gsk.com/investors/reps08/GSK-Report-2008-full.pdf
359. European Patent Office: Synergistic Combinations of Zidovudine, 1592U89 and 3TC or FTC. http://v3.espacenet.com/origdoc?DB=EPODOC&IDX=WO9630025&F=1&QPN=WO9630025
360. GSK withdraws Trizivir patent application 'in public interest,' www.livemint.com, 10 October 2007. http://www.livemint.com/2007/10/10005826/GSK-withdraws-Trizivir-patent.html
361. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
362. Antiretroviral Therapy of HIV Infection in Infants and Children: Towards universal access: Recommendations for a Public Health Approach 2006, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf
363. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
364. WHO Model list of Essential Medicines, 16th list, March 2009, World Health Organization, Geneva. http://www.who.int/medicines/publications/essentialmedicines/en/index.html
365. World Trade Organization: TRIPS and Public Health. http://www.wto.org/english/tratop_e/trips_e/public_health_e.htm
366. Neither Expeditious, Nor a Solution: The WTO August 30th Decision is Unworkable. Medecins Sans Frontieres Campaign for Access to Essential Medicines, 2006. http://www.accessmed-msf.org/fileadmin/user_upload/medinnov_accesspatents/WTOaugustreport.pdf
367. Antiretroviral Therapy of HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach, 2006 revision, World Health Organization, Geneva. http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf
368. Report of the WHO Paediatric Working Group: Preferred antiretroviral medicines for treating and preventing HIV infection in younger children, 2007, World Health Organization, Geneva. http://www.who.int/hiv/pub/paediatric/antiretroviral/en/index.html
369: Pharmaceutical Benefit Scheme Australia. http://www.pbs.gov.au/html/healthpro/home (accessed 28.8.09).
370: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm
371:http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm135125.htm
372. Addendum to 2006 WHO Guidelines on antiretroviral therapy for HIV infection in adults and adolescents. http://www.who.int/hiv/art/ARTadultsaddendum.pdf
373. Ford at all, 2007. Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand. AIDS 2007, 21 (suppl 4):S21-S29
374. http://www.apotex.com/apotriavir/default.asp
375. Rapid Advice: Antiretroviral therapy for HIV infections in adults and adolescents, Nov 2009. http://www.who.int/hiv/pub/ARV/rapid_advice_art.pdf

Abbreviations

3TC lamivudine; nucleoside analogue reverse transcriptase inhibitor.

ABC abacavir; nucleoside analogue reverse transcriptase inhibitor.

AIDS Acquired Immune Deficiency Syndrome

ALP AIDS Law Project

ANVISA Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil)

API active pharmaceutical ingredient

ARIPO African Regional Intellectual Property Organisation. There are currently sixteen states which are party to the Lusaka Agreement and therefore members of ARIPO. These are: Botswana, the Gambia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Sierra Leone, Somalia, Sudan, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe (Total: 16 Member States).

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 programs.

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

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

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.

EU European Union

EXW "Ex-works". A commercial term (incoterm) meaning that the seller delivers when he places the goods at the disposal of the buyer at the seller's premises or another named place (i.e. works, factory, warehouse etc.) not cleared for export and not loaded on any collecting vehicle.

FDA United States Food and Drug Administration

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

FOB "Free on board". A commercial (incoterm) term meaning that the seller delivers when the goods pass the ship's rail at the named port of shipment. This means that the buyer has to bear all costs and risks of loss or damage to the goods from that point. The FOB term requires the seller to clear the goods for export.

FPV fosamprenavir

FTC emtricitabine; nucleoside analogue reverse transcriptase inhibitor

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

GPRM WHO Global Price Reporting Mechanism 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

MVC maraviroc

NDRA National Drug Regulatory Authority

NFV nelfinavir; protease inhibitor

NGO Non-Governmental Organisation

NIH National Institutes of Health

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI Nucleoside Analogue Reverse Transcriptase Inhibitor

NtRTI Nucleotide Reverse Transcriptase Inhibitor

NVP nevirapine; non-nucleoside analogue reverse transcriptase inhibitor

OAPI Organisation Africaine de la Propriété Intellectuelle, African Intellectual Property Organisation, 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 low-dose ritonavir, used as a booster

R&D Research and Development

RAL raltegravir

RTV ritonavir; protease inhibitor

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

WHO GPRM WHO Global Price Reporting Mechanism

WTO World Trade Organization

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

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