UNTANGLING THE WEB OF

ANTIRETROVIRAL PRICE REDUCTIONS

18th Edition – July 2016

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

www.msfaccess.org

PREFACE

In this report, we provide an update on the key facets of HIV treatment access. It includes the latest HIV treatment guidelines from World Health Organization (WHO), an overview on pricing for first-line, second-line and salvage regimens, and a summary of the opportunities for – and threats to – expanding access to affordable antiretroviral therapy (ART). There is a table with information on ARVs, including quality assurance, manufacturers and pricing on pages 55 to 57.

THE MSF ACCESS CAMPAIGN

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

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MSF AND HIV

Médecins Sans Frontières (MSF) began providing antiretroviral therapy to a small number of people living with HIV/AIDS in 2000 in projects in Thailand, South Africa and Cameroon. At the time, treatment for one person for one year cost more than US$10,000. With increased availability of low-cost, quality antiretroviral drugs (ARVs), MSF provides antiretroviral treatment to 240,100 people in 18 countries, implements treatment strategies to reach more people earlier in their disease progression, and places people living with HIV at the centre of their care.

Over the past 16 years, the MSF Access Campaign has been monitoring the barriers to availability and affordability of life-saving ARVs and appropriate formulations, including patent monopolies, prices and lack of generic competition through *Untangling the Web,* and pushing for the uptake of policies that promote access to affordable quality medicines. Due primarily to generic competition, the price of ARVs has dropped by more than 99% over the last 15 years, but the price of the newest drugs, already needed by some people in MSF projects, is prohibitive and a source of great concern both for MSF and national treatment programmes.

PATENT OPPOSITION DATABASE

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

www.patentoppositions.org

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STATE OF HIV TREATMENT ACCESS

In 2000, when the International AIDS Conference was last held in Durban, South Africa, a basic antiretroviral (ARV) regimen cost over US$10,000 per person per year (PPPY), multilateral programmes funding the fight against HIV, TB, and malaria did not exist, and many donors – such as the US government – had yet to provide a single dollar for antiretroviral treatment in resource-limited countries.

Now, in 2016, 17 million HIV-positive people are receiving lifesaving antiretroviral therapy (ART),[1] and the lowest price for a generic, World Health Organization (WHO)-recommended first-line regimen is $100 PPPY.

In 2015, the number of people starting HIV treatment surpassed the number of new infections in Africa for the first time. Since 2010, the number of people receiving ART has more than doubled.[1,2] The push to continue ARV scale-up has gained momentum around the UNAIDS global targets for 2020, referred to as '90-90-90'.[3] To meet these targets, the number of people on treatment will need to more than double again, since nearly 20 million HIV-positive people are newly eligible for ART under the new WHO 'treat-all' recommendation.[1]

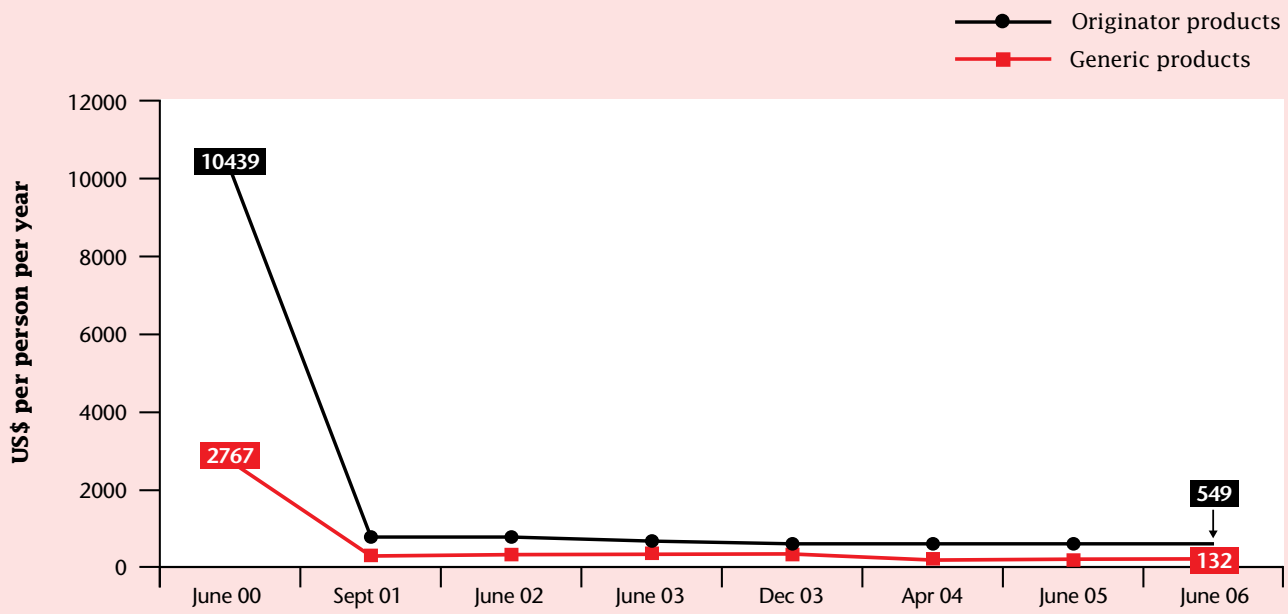
At the UN High Level Meeting on HIV in June 2016, governments agreed on a global target: reaching 30 million people with treatment by 2020. Reaching this goal will require increased and sustained support from donors.

THE 2020 UNAIDS TARGET: 90-90-90

By 2020, 90% of all HIV-positive people will be aware of their status; 90% of all people diagnosed with HIV will have access to sustained ART; and 90% of people on ART – or 73% of all HIV-positive people – will achieve viral suppression.[3]

Tsandia receives her antiretroviral medicines at the HIV department of the Arua Regional hospital in Uganda.

GRAPH 1: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTION FOR A FIRST-LINE REGIMEN



Since 2000, MSF has been providing HIV care and treatment to people in developing countries. Today, MSF provides HIV treatment for over 240,000 people.

SPEED UP TREATMENT SCALE-UP IN WESTERN AND CENTRAL AFRICA

Although HIV prevalence is lower in Western and Central Africa than in Southern Africa, over a quarter of all AIDS-related deaths occur in the region, including 40% of all deaths among children.[4]

In Central African Republic, HIV prevalence is 5%, but HIV accounts for 84% of hospital-based deaths in places where MSF works. In Democratic Republic of the Congo, three out of four HIV-positive people who present to the hospital where MSF works are too sick to save.

In 2015, only 1.8 million people (28%) of the region's 6.5 million HIV-positive people were accessing ART.[1] Political instability, inadequate funding and weak healthcare systems - some worsened by the Ebola outbreak - add to barriers that include limited access to diagnostic and monitoring tests, drug stockouts, out-of-pocket fees for healthcare, and lack of decentralised treatment.[4]

Mohamed (left) is tested for HIV at an MSF mobile clinic in Conakry, Guinea.

OPTIMISING HIV TREATMENT

COUNTRIES SHOULD IMPLEMENT WHO GUIDELINES

Immediate treatment and a steady supply of affordable medicines are essential to curbing the HIV epidemic. ART lowers the risk of serious illness and death, reduces the risk of developing tuberculosis (TB) by 65%, and reduces HIV transmission by 96%.[5,6,7,8]

In light of the individual and community benefits of HIV treatment, WHO has recommended immediate and lifelong ART for everyone with HIV: all infants, children, adolescents, and adults, including pregnant and breastfeeding women, regardless of CD4 cell count or disease stage.[9]

In June 2016, WHO issued new HIV treatment guidelines, including recommendations for new ARV regimens and differentiated models of care that put the patient at the centre of their treatment.[10]

Countries should implement the WHO recommendations, including 'test and start', routine viral load monitoring **[see below]**, better drugs (new ARVs and once-daily, fixed-dose combinations), adherence support, and differentiated models of care to facilitate rapid scale-up and quality patient care.[10]

ROUTINE VIRAL LOAD MONITORING

Access to viral load testing – the gold standard for HIV treatment monitoring – is essential to achieving the 90-90-90 targets. For infants, an early diagnosis can be life-saving – and requires viral load testing. In 2016, WHO recommended point-of-care viral load testing for HIV-exposed infants.[10]

Since 2013, WHO has recommended routine viral load monitoring for diagnosing HIV treatment failure; the 2015 guidelines recommend viral load monitoring – now with dried blood spot testing – at six and 12 months after starting ART. For stable patients, viral load monitoring is recommended once every year thereafter instead of CD4 cell count monitoring.[9,10]

As tests have become more affordable and rollout less complex, more countries have adopted routine viral load as part of national policy. However, implementation still lags far behind; a 2014 WHO study of 122 low- and middle-income countries found that only 22% of people on ART received viral load monitoring.[11]

MSF began implementing viral load testing in 2012. In Lesotho, Malawi, Mozambique, Swaziland, Uganda, and Zimbabwe, risk factors for having a detectable viral load have been identified, leading to interventions including a child-friendly clinic, community ART groups and enhanced adherence counselling. Routine viral load testing has triggered a switch to second-line treatment and enhanced adherence counselling in 10% to 68% of patients.[12]

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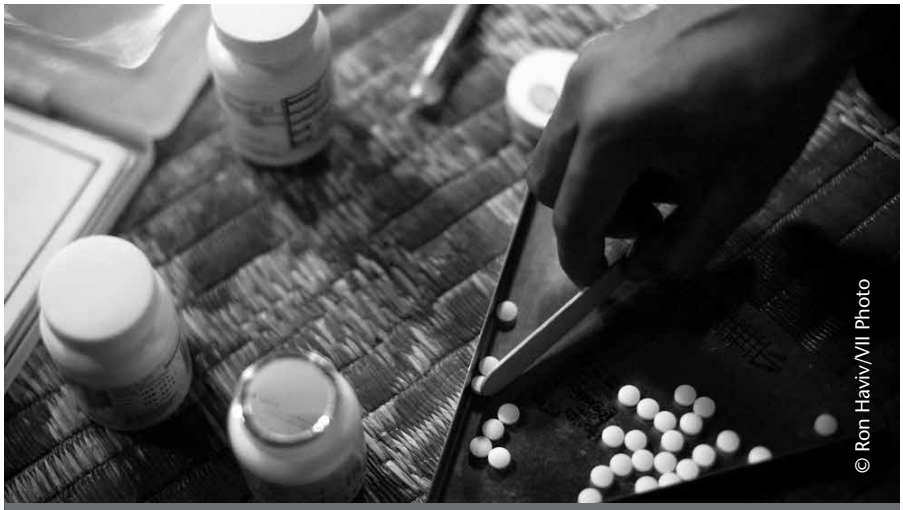
People wait to have their blood tested to measure their viral load at the HIV department of Arua Regional Hospital in Uganda.

IMPROVING FIRST-LINE TREATMENT



An MSF outreach worker measures out antiretroviral medication during a home visit in Dawei, in southeastern Myanmar.

The 2015 WHO HIV treatment guidelines added recommendations for two alternative first-line ARVs: dolutegravir (DTG), a well-tolerated integrase inhibitor that rapidly lowers HIV viral load and is robust, with very few documented cases of resistance,[13] and a lower, equally effective dose of efavirenz (EFV; 400mg vs. 600mg)[9] that is better tolerated than the higher dose.[14] Before these ARVs become part of a preferred first-line regimen, additional clinical data on their safety and efficacy during TB treatment, pregnancy, and breastfeeding are needed;[9,15] these studies are planned or underway.

BETTER SECOND-LINE TREATMENT

As access to viral load monitoring increases, more people in need of second-line treatment will be identified. The WHO treatment guidelines have added two alternative recommendations for second-line ART: a heat-stable, fixed-dose combination (FDC) of darunavir/ritonavir (DRV/r) and a two-drug regimen of raltegravir (RAL; an integrase inhibitor) with lopinavir/ritonavir (LPV/r).[10]

DRV is a boosted protease inhibitor (PI) with fewer side effects than the other second-line protease inhibitors (although it cannot be used during rifampicin-based TB treatment).[16,17,18] But access to DRV/r is limited; there is no quality-assured heat-stable FDC on the market, and the current price of generic DRV alone is at least three times more than other protease inhibitors, making it costly for wide-spread use.

Loved Mupandanana is HIV positive, and her first-line treatment for HIV seems to be failing. At Gombe clinic, in Manicaland Province in Zimbabwe, she is receiving counselling about the need to move on to second-line treatment.

In 2015, MSF provided second-line HIV treatment for 9,700 people.

Continued overleaf

THE ARV PIPELINE FOR ADULTS

The ARV pipeline includes new drug formulations and classes. Tenofovir alafenamide (TAF), a new prodrug of tenofovir disoproxil fumarate (TDF), is equally effective as the currently available version, at one-tenth of the dose. TAF is likely to be safer, and should be significantly less expensive to produce than TDF,[19] but data on drug interactions between TAF and TB treatment are needed.

The United States Food and Drug Administration (USFDA) has approved three TAF-based FDCs (in November 2015, March 2016 and April 2016). Stand-alone TAF has been approved in Europe (and filed in the US) for hepatitis B treatment only. If Gilead, the company marketing TAF, does not register the drug as a single ARV for use in HIV, generics manufacturers may face complications and long delays in registering TAF-containing FDCs in other countries.

Long-acting, injectable ARVs with monthly or bi-monthly dosing could improve adherence and significantly reduce the cost of HIV treatment; interim results from a trial of a long-acting injectable combination (rilpivirine and cabotegravir) are promising, although an interaction between cabotegravir and rifampicin requires further study.[20,21,22,23]

New ARV classes include attachment and maturation inhibitors; there are also new versions of integrase inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in development.

THE ARV PIPELINE FOR CHILDREN

Only 49% of the world's HIV-positive children had access to treatment in 2015.[24] Without treatment, over half of all HIV-positive children die before their second birthday;[25] treating infants when they are less than 12 weeks old lowers mortality by 75%.[26]

Research and development of paediatric ARVs and FDCs has lagged far behind adult treatment, which has severely limited treatment options for HIV-positive infants and children.

There is a new pellet formulation of LPV/r, which is part of the WHO-recommended first-line regimen for children under three years old.[10] In May 2015, the USFDA granted tentative approval for LPV/r pellets for children who weigh >5 kg and are over 14 days old.[27,28] This formulation of LPV/r is available to a limited group of low- and middle-income countries through a Medicines Patent Pool (MPP) voluntary licence (VL), although one year after stringent regulatory authority (SRA) approval, it has not yet been made commercially available.

Pellets could replace LPV/r syrup, which contains 40% alcohol and propylene glycol, requires refrigeration, and has been described as tasting "horrible"[29] – all of which have made treating young children difficult. The price of the pellets needs to be reduced so it is at least on par with the syrup, to encourage countries to adopt them.

The Drugs for Neglected Diseases *initiative* (DND*i*) LIVING study is looking at the safety, effectiveness and acceptability of LPV/r pellet-based therapy in infants (>four weeks old) and children, with enrolment having begun in Kenya.[30]

In 2015, MSF supported treatment for 6,800 HIV-positive pregnant women, and post-exposure treatment for 4,400 babies.

Jennipher Mwamvera is a mother of four and a patient in the prevention-of-mother-to-child transmission of HIV (PMTCT) program in Thyolo, Malawi.

PRICING

Affordable generic ARVs have made HIV treatment scale-up possible in countries that can access them. Robust competition between multiple generics producers has dramatically lowered the price of first-line antiretroviral therapy over the last decade-and-a-half.

FIRST-LINE REGIMENS

Since 2014, there has been a 30% reduction in the price for generic first-line treatment.* If countries are able to import and use generics, the price for the WHO-recommended, fixed-dose combination of tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) can be as low as $100 PPPY, down from $143 PPPY in 2014.

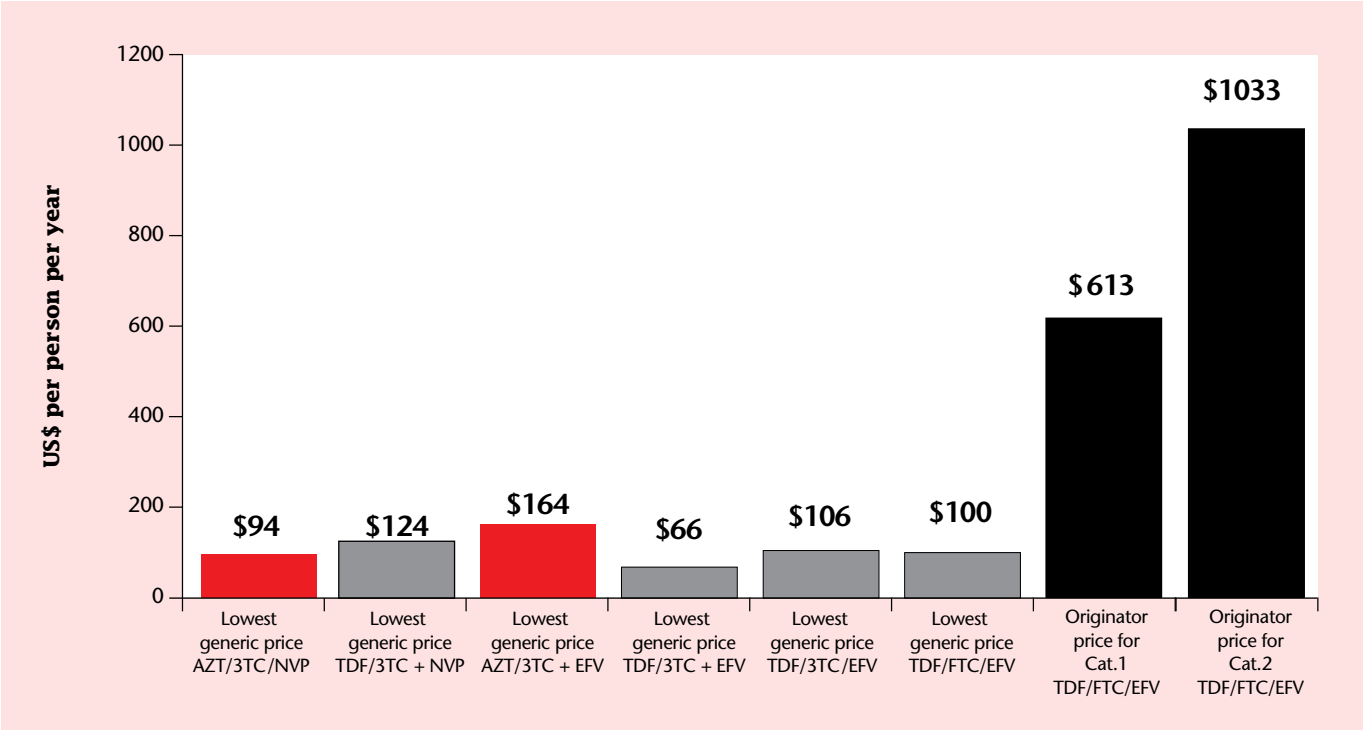
Prices for first-line treatment are unlikely to decrease further, since they are now close to the minimum sustainable production price, according to experts.[31]

Aurobindo's generic version of dolutegravir will have a price of $44 PPPY,[32] which is on par with the price of efavirenz 600mg.

A fixed-dose combination of DTG with TDF/XTC should be available by the end of 2017.

Continued overleaf

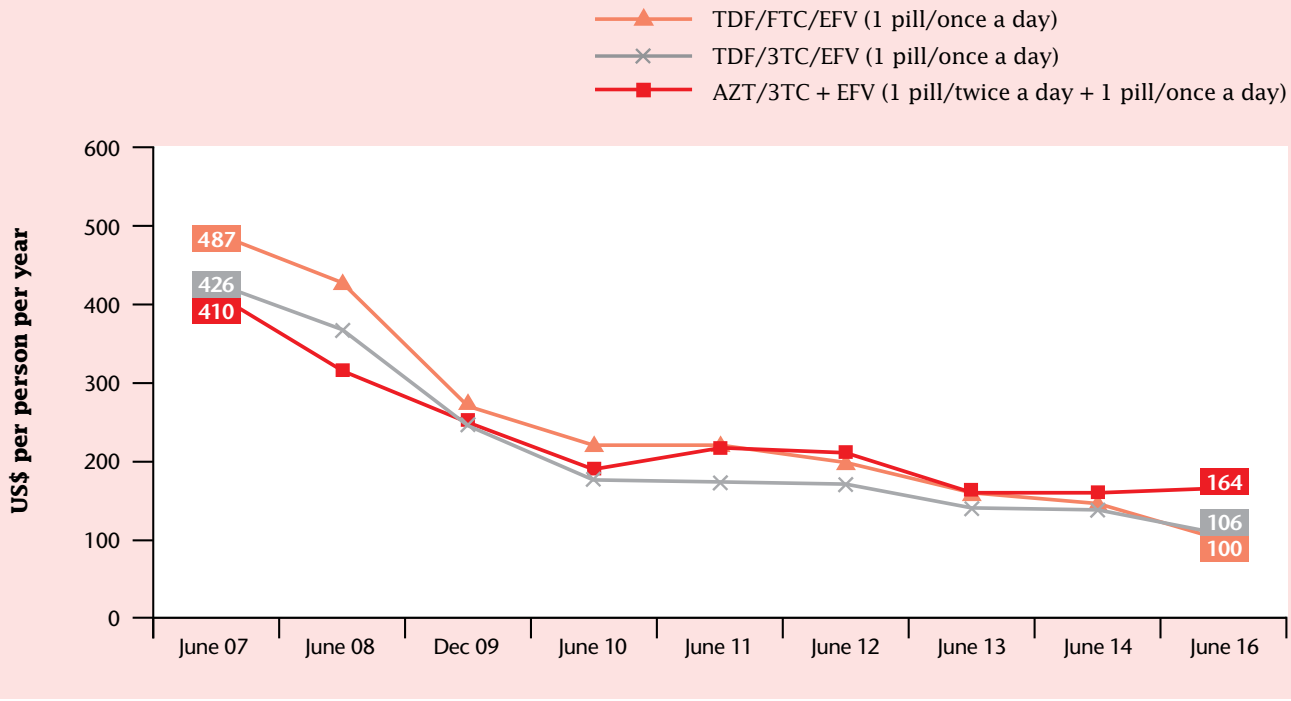
GRAPH 2: THE PRICES OF DIFFERENT FIRST-LINE REGIMENS TODAY



* Price reductions may be due in part to currency fluctuations.

Pricing continued

GRAPH 3: THE EVOLUTION IN PRICE OF DIFFERENT FIRST-LINE REGIMENS



HIGH ANTIRETROVIRAL PRICES IN MIDDLE- AND HIGH-INCOME COUNTRIES

According to UNAIDS, 70% of all HIV-positive people will be living in middle-income countries by 2020.[33]

Several ARVs are still on patent in middle-income countries. Some lower- and upper-middle-income countries where patent barriers on key ARVs remain cannot produce or buy generic ARVs, because they are not included in voluntary licensing agreements, and/or have not used TRIPS flexibilities such as compulsory licences.* Instead, they must pay high prices to originator companies for patented drugs on a case-by-case basis or under 'tiered pricing' schemes that are not based on a realistic concept of affordability.[34]

High-income countries such as the US are struggling with spiralling costs of patented medicines, including ARVs. In the US, the combination of TDF/FTC/EFV (sold under the brand name Atripla) costs nearly $30,000 PPPY[35] versus $100 PPPY for Indian generic versions.

* The World Trade Organization's Trade-Related Aspects of Intellectual Property (TRIPS) Agreement can and should be interpreted in light of the goal "to promote access to medicines". Legal safeguards include (but are not limited to) enabling networks of people living with HIV/AIDS to challenge patent claims before and/or after they are granted; the right to examine patent claims strictly and reject new use and/or new forms of known medicines; the right to register generic versions of patented medicines; the right to issue compulsory licences (CLs; these allow countries to import or locally produce generic versions of patented medicines without the patent holder's consent); and the right to import and resell lower-priced medicines from other countries instead of paying higher prices for them – also without consent from the patent holder (called parallel importing).

SECOND-LINE REGIMENS

Boosted protease inhibitors are the backbone of second-line regimens. The lowest-priced generic second-line regimen, zidovudine/lamivudine (AZT/3TC) and atazanavir/r (ATV/r), is now priced at $286 PPPY. Since 2014, the price has dropped by 11%, from $322 PPPY.

Switching to second-line therapy nearly triples the price of treatment **[see graph 5]**. Currently, there are two WHO-preferred boosted protease inhibitors for second-line regimens, ATV/r and LPV/r; one alternative boosted protease inhibitor, darunavir+r (DRV+r); and an alternative, twice-daily two-ARV regimen, the integrase inhibitor raltegravir (RAL) plus LPV/r.[10]

A generic, fixed-dose, heat-stable formulation of ATV/r is available. It has fewer side effects than LPV/r, although it cannot be used during rifampicin-based TB treatment. Because of supply problems with LPV/r, an increase in demand for ATV/r is expected, hopefully leading to lower prices.

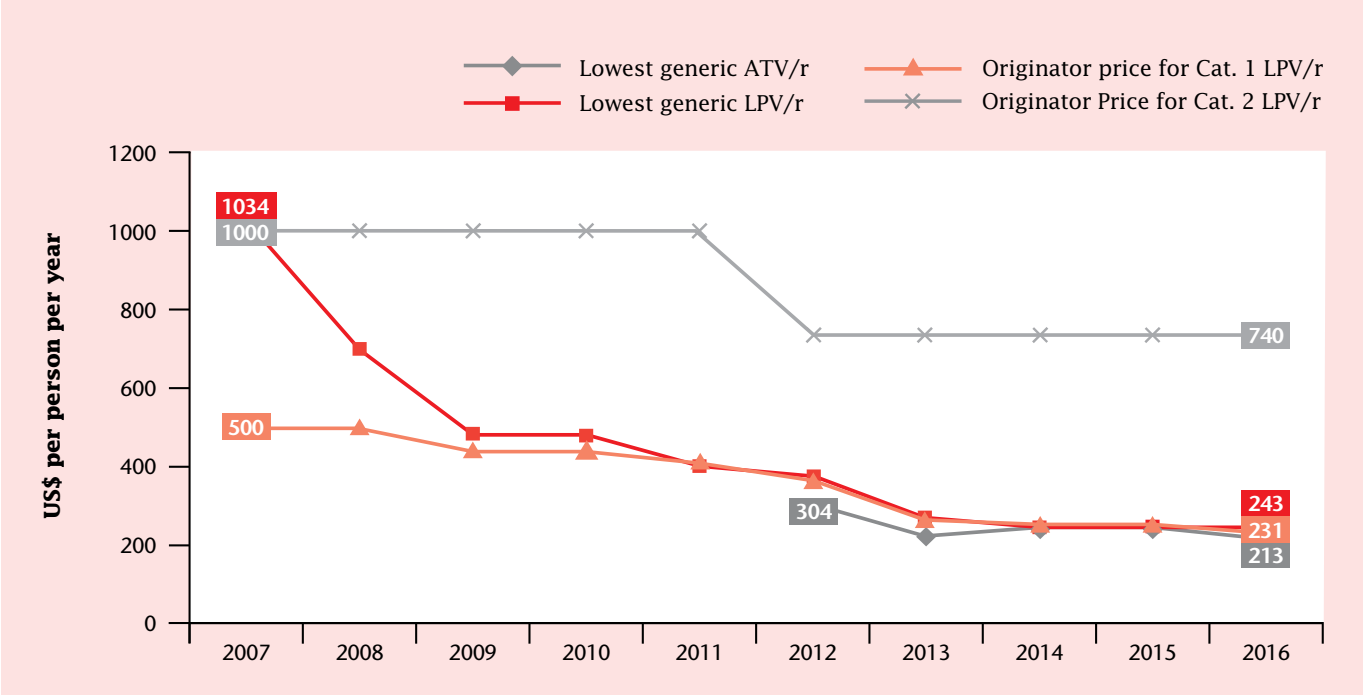
Although LPV/r must be taken twice a day, it can be dose-adjusted for use with rifampicin-based TB treatment. LPV/r is still more expensive than ATV/r, at $243 PPPY versus $213 PPPY **[see graph 4]**. The price of generic LPV/r is 5% higher than the originator product, because the originator company, AbbVie, has been consistently undercutting generic competition with slightly lower prices.

For several of the newer second-line options, current demand is low. The price of generic versions has not yet come down, and only a few producers have entered the market. DRV is much more expensive than ATV/r or LPV/r, and it is not available as a fixed-dose combination with ritonavir (RTV or r). Darunavir is available from the originator for $663 PPPY; generic versions are $1217 PPPY, since the current low demand prevents companies from being motivated to commercialise it in low- and middle-income countries.

Prices for boosted protease inhibitors are especially high in middle-income countries, since many of them have patent barriers and are excluded from voluntary licensing agreements. In its designated Category 2 countries,* AbbVie charges higher prices for LPV/r than in least-developed countries (LDCs): $740 PPPY (which has not changed since 2012), compared to $231 PPPY in LDCs **[see graph 4]**. In Malaysia, prices for LPV/r were quoted above $3,500 PPPY in 2014.[36] The originator price from Bristol-Myers Squibb (BMS) for atazanavir– which must be used with ritonavir (RTV) – is $816 PPPY; AbbVie's originator price for RTV is set on a "case-by-case" basis.

The lowest originator price for RAL is $675 PPPY; the lowest-price generic version is $973 PPPY **[see graph 6]**. Currently, RAL is taken twice daily, however, Merck plans to submit data to the USFDA and the European Medicines Agency (EMA) to seek approval for once-daily RAL.[37] RAL can be dose-adjusted for use during rifampicin-based TB treatment.[38]

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



* Albania, Armenia, Azerbaijan, Belarus, Bolivia, Bosnia and Herzegovina, China, Colombia, Dominican Republic, Ecuador, El Salvador, Fiji, Georgia, Guatemala, Guyana, Honduras, India, Indonesia, Jamaica, Jordan, Kazakhstan, Kyrgyzstan, Macedonia, Marshall Islands, Micronesia, Moldova, Mongolia, Montenegro, Nicaragua, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Serbia, Sri Lanka, Suriname, Syria, Tajikistan, Thailand, Tonga, Turkmenistan, Ukraine, Uzbekistan, Viet Nam.

Continued overleaf

Pricing continued

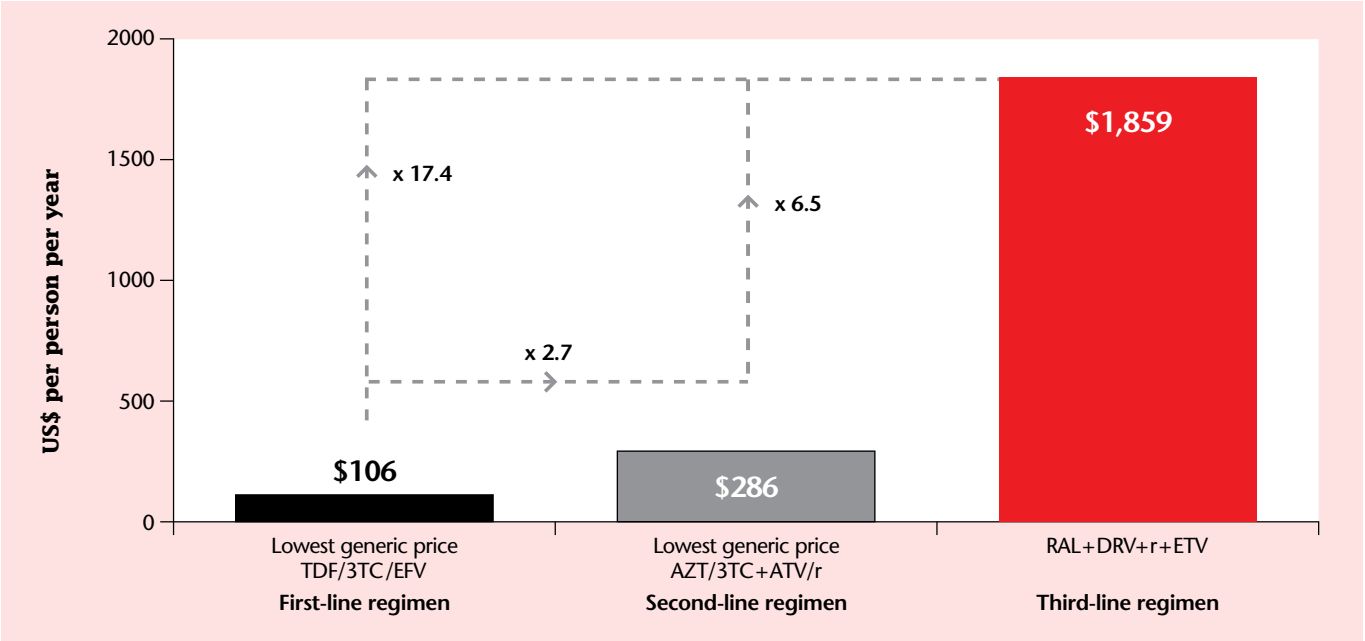
SALVAGE REGIMENS

There is an urgent need for more affordable third-line or salvage regimens for people that have developed resistance to first- and second-line treatment. Low volume and high prices from both originator and generic companies keep these medicines out of reach.

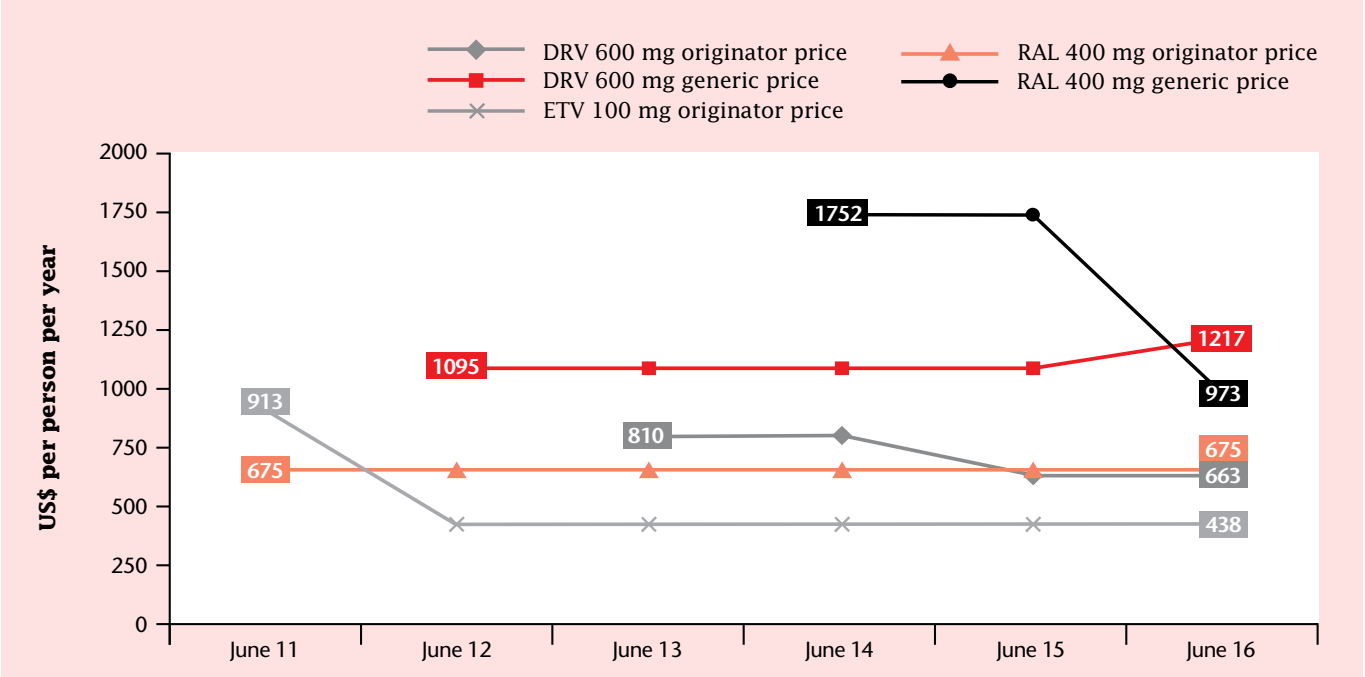
The lowest price for a salvage regimen today is $1,859 PPPY, for darunavir+r, raltegravir and etravirine (DRV+ r + RAL + ETV), in countries that fall into the select group eligible for access pricing from originators, but many countries are paying much more. This represents nearly an 18-fold increase over the lowest first-line prices, and nearly a seven-fold increase over the most affordable second-line regimen **[see graph 5]**.

Since 2014, the price of generic DRV has increased by 10%, from $1,095 to $1,217; this does not include the ritonavir it must be used with. At the same time, the access price from the originator has dropped by 17%, from $810 to $675. A quality-assured generic RAL is priced at $973 PPPY, but it is still more expensive than the originator version, which has stayed at $675 since 2011. The originator price for ETV has stayed at $438 since 2011 **[see graph 6]**.

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



GRAPH 6: PRICES FOR THIRD-LINE ARVS



REGISTRATION

In many countries, marketing authorisation for promising new ARVs can take several years; this type of regulatory lag forces people living with HIV/AIDS to wait for life-saving medicines. National Drug Regulatory Authorities (NDRAs) do not always have the resources to ensure timely registration of more affordable generic versions of new ARVs, and/or fail to prioritise them.[39]

Pharmaceutical companies often don't prioritise registration in low- and middle-income countries. Some originator companies shift the responsibility for filing registration dossiers in high-burden developing countries to generics companies that have signed voluntary licences.

In some countries, generics companies are able to register generic versions of medicines, but in others, when originators don't register their ARVs before generics companies do, it may cause significant delays or become an absolute barrier to treatment access.

Countries have different regulatory pathways, priorities, rules, requirements, legal frameworks, capacities, and timelines, and some do not have NDRAs. There is no 'essential documentation package' to streamline the registration process across all NDRAs in developing countries, and country-level bureaucracy can delay registration.

Collaborative or regional registration processes have reduced the time to registration for some products in some participating countries. These collaborations should be considered by national regulatory authorities to reduce the considerable workload associated with reviewing registration dossiers. For example, in East Africa, a pilot of the African Medicines Registration Harmonisation Initiative has reduced the time to registration by 50% in Burundi, Kenya, Rwanda, Uganda, and Zanzibar.[39]

India's lack of intellectual property (IP) barriers and historically efficient regulatory pathway made it possible for generics companies to produce and register more affordable medicines for developing countries. But availability of new quality-assured generic ARVs and FDCs from India is starting to be delayed. This is partly because India's criteria to waive phase III clinical trials are restrictive in certain cases. These criteria need to be expanded to include new drugs for neglected diseases, ARVs for paediatrics, and salvage regimens. In addition, the Indian NDRA should prioritise new ARVs, FDCs, and child-friendly formulations, taking note of, and relying on WHO guidelines and/or Expression of Interest from the WHO prequalification programme.*

Another delay is the WHO prequalification programme, which has been essential for reviewing the quality, safety, and efficacy of generic ARVs that aren't always reviewed or approved by a stringent regulatory authority (SRA). The median time to WHO prequalification is 200 days.[66]

97% of the medicines MSF uses to treat people with HIV are generics made in India.

BARRIERS TO UNIVERSAL ACCESS TO GENERIC DOLUTEGRAVIR FROM INDIA

The pharmaceutical company ViiV has granted voluntary licences (VLs) for the integrase inhibitor dolutegravir (DTG) to several Indian generic companies through the Medicines Patent Pool (MPP). The VLs will not result in universal access to the drug, since a number of high-burden countries are excluded from the territories that can import the generic version of DTG from India.

In India, generic DTG will only be available on the public market or to non-governmental providers, leaving a number of drug-resistant patients who need immediate access without any source of generic DTG from Indian pharmacies.

Although DTG has been registered in many other countries, ViiV, the originator company, has not filed for registration in India. As a result, the responsibility for registration is now with Indian producers that have developed generic dolutegravir. They will need to do local clinical trials, as per the Indian NDRA requirements for new drugs, which will lead to a significant delay in the availability of affordable generics across the developing world. In the meantime, patients in India who have exhausted other treatment options are left without access to DTG, since ViiV has been dragging its feet to provide the medicine via compassionate use.

To ensure open generic competition in the future, a patent opposition for DTG has been filed in India, by and on behalf of people living with HIV, and supported by MSF.

* These include: dolutegravir (DTG) singles and FDCs, including tenofovir/lamivudine/dolutegravir; a low-dose (400mg) efavirenz FDC and heat-stable darunavir/ritonavir Priority paediatric formulations for HIV include: lopinavir/ritonavir pellets or sachets; abacavir/lamivudine/lopinavir/ritonavir (ABC/3TC/LPV/r) zidovudine/lamivudine/lopinavir/r (AZT/3TC/LPV/r) pellets or sachets for children over three years old and lamivudine/abacavir/efavirenz (3TC/ABC/EFV 75/150/150mg) dispersible tablets for children ages 3-10 years.

PATENT OPPOSITIONS AND PATENT LAW REFORM

INDIA, THE 'PHARMACY OF THE DEVELOPING WORLD', IS UNDER PRESSURE TO DROP ITS PUBLIC HEALTH SAFEGUARDS

Indian generics comprise 76% of the ARVs used in low- and middle-income countries and more than 97% of those used by MSF in its treatment programmes.[31,44] India encouraged generic competition for decades, since it did not introduce patents for pharmaceuticals until 2005 (when it had to comply with international trade rules under the World Trade Organization [WTO] Agreement on Trade-related Aspects of Intellectual Property Rights [TRIPS]). India's national patent laws include public health safeguards such as stringent patentability criteria and the opportunity to file legal challenges to patents before and/or after they are granted (called pre-and post-grant patent oppositions).

India has fought off numerous challenges to its public health safeguards, but it has been under excessive external and domestic pressure – led by the multinational pharmaceutical lobby – to change its national intellectual property laws and policies, or sign free trade agreements that will dismantle them. Over the last two years, pharmaceutical industry-led pressure from the US has been escalating. India must reject the demands to grant patents more easily, as well as TRIPS-plus rules that the United States is trying to force upon India's Ministry of Commerce.

PATENT OPPOSITIONS FOR HEPATITIS C

Patent oppositions have been used when patent claims do not meet national patentability criteria, and when a patent directly blocks or delays access to essential medicines.

Worldwide, an estimated 80-100 million people have chronic hepatitis C virus infection;[45] without treatment, they are at risk of developing liver failure and liver cancer.

Hepatitis C can be cured with a few months' treatment using oral drugs, called direct-acting antivirals (DAAs). In 2013, the price of the first DAA on the market, sofosbuvir, sent shock waves throughout the world. Although it can be mass-produced for less than $1 per pill,[46] sofosbuvir's launch price was $1,000 per pill in the US.

Gilead's patent on sofosbuvir has been opposed – and rejected – in some countries. The patent on the pro-drug form of sofosbuvir was rejected in China and Ukraine. In Egypt, where the primary patent application for sofosbuvir was rejected, a company called Pharco has applied for WHO prequalification for their generic version of the drug.

In India, one critical sofosbuvir patent has been recently granted, reversing its prior rejection in 2015. This decision is now under appeal. If upheld, the patent will block additional competition from the Indian generics companies that do not want to sign a voluntary licence with Gilead, leaving them unable to supply sofosbuvir to millions of people in India and other middle-income countries. In addition, this decision would allow Gilead to disrupt or stop exports of the raw materials from India that are used to make sofosbuvir's key active pharmaceutical ingredient (API). This will make it difficult for the generics companies in Bangladesh, Egypt, Latin America and Pakistan that are producing sofosbuvir without a patent in force – and without a licence agreement with Gilead – to continue production. More patent oppositions on sofosbuvir have been filed in Argentina, Brazil, France, India, Russia and Thailand.

PATENT LAW REFORM IN SOUTH AFRICA, BRAZIL AND ARGENTINA

South Africa and Brazil are in the process of reforming their patent laws, in part to more effectively manage prices for medicines, and to encourage competition (and local production). There is a lot at stake: South Africa has the largest number of people living with HIV in the world, and Brazil guarantees HIV treatment for all, with many people on salvage therapy, as well as first- and second-line treatment. But delays in patent law reform will undermine access to affordable medicines, including ARVs.

SOUTH AFRICA

In 2015, 3.1 million people living with HIV were accessing antiretroviral therapy through South Africa's public sector,[47] and the government recently announced a 'test and start' policy.[48] As more people are treated, the need for second-line and salvage regimens will increase. Many of these ARVs are patented and are too expensive for the government to procure for the public sector. But South Africa has not introduced or implemented key measures to safeguard public health, including fully adopting TRIPS flexibilities and, especially, substantive examination of patent claims. In 2008 alone, South Africa granted 2,442 patents, while Brazil granted only 272 patents between 2003 and 2008.[49]

In 2009, South Africa's Department of Trade and Industry (DTI) initiated a process to reform the country's IP law and policy. In 2011, TAC, Section 27 and MSF co-launched the 'Fix the Patent Laws' campaign, which now includes 18 other non-governmental organisations. The campaign highlights how pharmaceutical companies have used evergreening tactics to exploit South Africa's patent system. In September 2013, the DTI released a draft policy document for public comment. But the new policy is still not finalised, and is not expected until mid-2017.

The longer DTI delays, the longer it will take for South Africa to introduce short- and long-term reforms that can accelerate and promote generic competition, and drive down prices for patented drugs. The delay also raises concern about undue political and commercial pressure from multinational pharmaceutical corporations involved in the 'Pharmagate' scandal (a covert $600,000 campaign funded by large pharmaceutical corporations and medical device producers to delay - and influence - South African patent reforms). South African Health Minister Aaron Motsoaledi has accused the multinational pharmaceutical companies in South Africa of conspiring against the state and the people of South Africa, and called on all South Africans to fight back "…to the last drop of their blood."[50]

BRAZIL

Brazil is consistently excluded from voluntary licensing programmes, and therefore forced into tiered pricing schemes from originator companies that charge unaffordable prices.

In order to overcome IP barriers to generic competition, a coalition of civil society groups recently filed a patent opposition in Brazil on the main patent related to TAF. In addition, in November 2015, GTPI (Working Group on Intellectual Property), a civil society coalition, filed a patent opposition to deny a patent to BMS (for atazanavir; ATV) that could extend the patent holder's monopoly until 2024. Brazil currently pays $496.40 PPPY for the 300mg version of ATV; a Health Ministry-approved licence between BMS and the Brazilian government-linked pharmaceutical laboratory Farmanguinhos forbids production of atazanavir in newer formulations and combinations, such as ATV/r.[51]

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MSF and the Treatment Action Campaign launched the 'Fix the Patent Laws' campaign to demand patient-focused reforms to South Africa's patent laws.

EVERGREENING

Many countries often do not examine patent claims strictly, leaving them vulnerable to 'evergreening', whereby pharmaceutical corporations make minor changes to medicines that are already on the market to extend their patents. Several ARVs should now be free from patent barriers (including ABC, DRV, EFV and RTV) since their basic patents have expired, but they are not – because of evergreening.

In Ukraine, home to nearly 265,000 people living with HIV,[40] GSK extended its abacavir (ABC) patent monopoly by eight years with its secondary patent on the hemisulfate salt.[41] Ukraine's price for originator ABC is $277.40 PPPY[42] versus $123.42 PPPY for the generic version.[43]

Continued overleaf

At the same time, multinational drug corporations are using lawsuits to challenge measures that promote generic competition in Brazil, including the country's patent examination process. Since 2001, ANVISA, Brazil's national drug regulatory agency, has participated in analysing pharmaceutical patent applications, instead of leaving this task exclusively to patent office examiners. ANVISA has rejected more than 400 of them. ANVISA's role in pharmaceutical patent examination has been considered an important safeguard to public health and access to medicines.[52] Multinational companies have frequently contested ANVISA's rejections in court. In 2011, the Attorney General's Office (AGU) issued a legal opinion strengthening the position of pharmaceutical corporations – although it proved unenforceable, the AGU has not formally withdrawn its legal opinion.

In November 2014, a multinational group of pharmaceutical companies (INTERFAMA, the Pharmaceutical Research Industry Association) filed a Collective Action against ANVISA, questioning the legitimacy of ANVISA's participation in the patent granting process. Local civil society groups have strongly reacted to these setbacks.

Patent law reform that would improve affordability of new medicines has been delayed for more than two years. In 2013, a 'package' of bills to amend Brazil's patent law was introduced. If approved, it will ensure that Brazil has clearer criteria for patent examination, and introduce important flexibilities into its national laws.[53]

ARGENTINA

Argentina has taken steps to improve its patent laws. In 2012, Argentina adopted new patentability examination guidelines for the pharmaceutical sector to prevent the granting of numerous patents that do not meet specific criteria such as novelty, inventive step, and industrial application. Since Argentina's new guidelines were enacted, 95% of ARV patent applications have been rejected, an increase from the 51% rejection rate in 2012.[54]

In 2015, CAEME – the association of multinational pharmaceutical corporations in Argentina – filed a court case questioning the validity of the patent guidelines. In response, civil society groups from Brazil and Argentina launched the 'Big Pharma Drop the Case' campaign at the 31st session of the UN Human Rights Council, to push CAEME and INTERFARMA to abandon their actions.

TRADE AGREEMENTS

Governments, civil society and generics producers should use TRIPS flexibilities to improve affordability of, and access to, needed medicines. But TRIPS flexibilities are endangered by free trade agreements (FTAs) that pose serious threats to access to affordable medicines. These FTAs include intellectual property provisions – so-called 'TRIPS-plus' provisions – that exceed countries' obligations under World Trade Organization (WTO) trade rules.

EU-INDIA FTA

Negotiations on the EU-India FTA began in 2007. They have been stalled since 2012, in part due to public pressure, but may resume this year. The EU-India FTA could jeopardise access to India's affordable generic medicines for millions of people by limiting production, sale and export of medicines in the future.

In the past, the EU has demanded a range of intellectual property provisions that exceed India's obligations under TRIPS, including measures that would allow companies to prevent legitimate export of medicines to developing countries or bring legal action against people who buy or distribute generics.[55]

TRANS-PACIFIC PARTNERSHIP AGREEMENT (TPP)

The TPP is a far-reaching trade agreement across the Asia-Pacific region. If ratified, the TPP will be the worst-ever trade agreement for access to medicines: it will lengthen, deepen and expand intellectual property and patent monopolies, and prevent or delay access to affordable, life-saving generic medicines for millions of people.[56] While the TPP agreement has been signed by governments, it has yet to be ratified by any country.

REGIONAL COMPREHENSIVE ECONOMIC PARTNERSHIP (RCEP)

The RCEP trade negotiations among 16 Asia-Pacific countries could threaten access to generic medicines due to the proposed inclusion of TPP-like intellectual property rules by Japan and South Korea.

Countries that did not join the TPP – particularly India and key members of the Association of Southeast Asian Nations – will be pushed to adopt similar standards in the RCEP negotiations, which would represent a rollback of protections against extended patent terms and data exclusivity that are part of past agreements.

The RCEP negotiations will have serious repercussions globally, since both India, the 'pharmacy of the developing world', and China, the world's largest producer of the active pharmaceutical ingredients (API) used to make medicines, are among the 16 countries included in the negotiations.

COLOMBIA: COMPULSORY LICENCE THREAT INVITES US PRESSURE

In April 2016, a leaked letter from the Colombian Embassy described how the US Senate Finance Committee and the United States Trade Representative were pressuring the Colombian government not to issue a compulsory licence* for the anti-cancer cancer drug imatinib.[58]

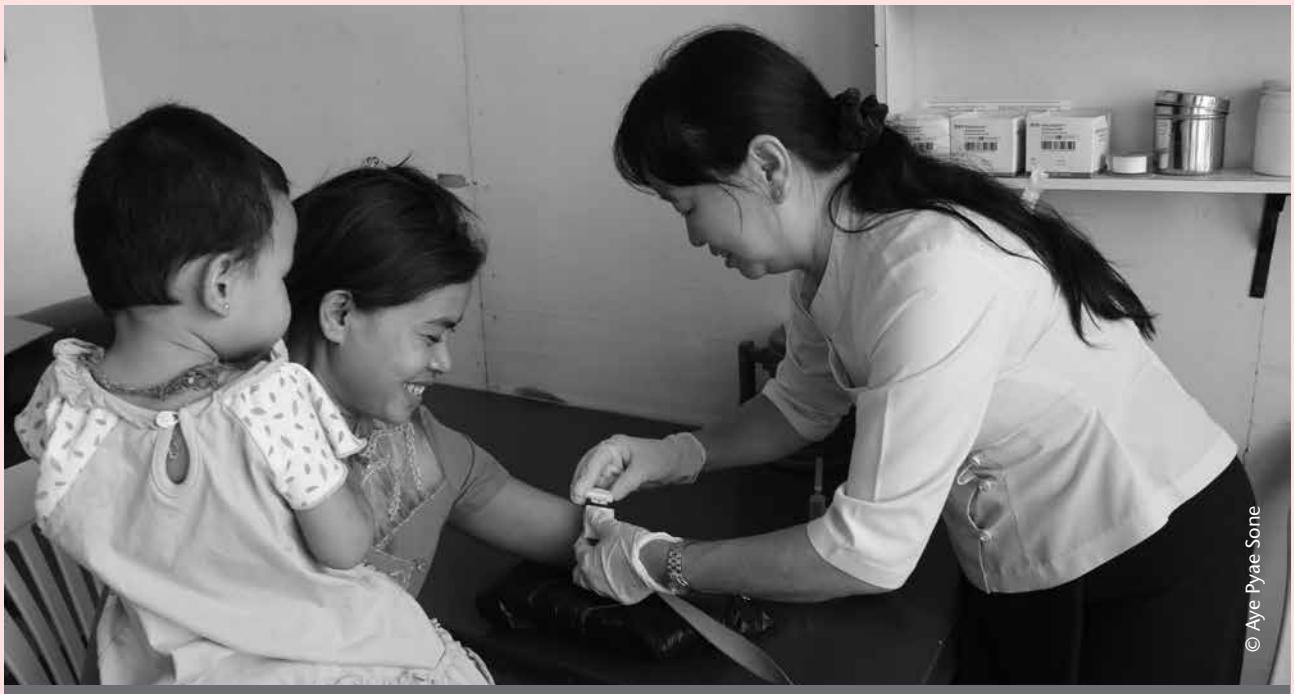
A number of countries have also faced similar pressure (Brazil, Ecuador and Thailand), which has discouraged other governments from issuing compulsory licences to ensure affordable medicines. As WHO states in its letter to Colombia's Minister of Health, "unaffordable high prices of essential medicines, including for non-communicable diseases, are a legitimate reason for issuing a compulsory licence".[59]

As of mid-June 2016, the Colombian Minister of Health announced that they had issued a 'public interest declaration' regarding imatinib, without public information about whether the government will issue a compulsory licence to allow manufacturing and import of price-lowering generic versions of the drug, or simply reduce the price of the Novartis product.[60]

LDC EXEMPTION FROM PHARMACEUTICAL IP EXTENDED

Least-developed countries (LDCs) have been granted an exemption from certain obligations under TRIPS, in recognition of their economic, financial and administrative constraints and their need to make or procure low cost generic medicines. Under this transition period, LDCs do not have to apply or enforce TRIPS provisions concerning patents (TRIPS section 5) or test data protection (TRIPS section 7) for pharmaceutical products until 1 January 2033.[57] But the free-trade agreements that are being negotiated in many countries across the Asia-Pacific region, in particular RCEP **[see Trade Agreements, page 14]**, could undermine the LDC transition period, unless UN agencies and civil society provide technical and political support to negotiating countries, particularly LDCs, to protect their TRIPS flexibilities in complex FTA negotiations.

LDCs in Asia, including Bangladesh, Cambodia, Laos and Myanmar, as well as countries in sub-Saharan Africa, should continue to use the waiver to the fullest extent possible to improve access to medicines and should resist any pressure to prematurely introduce intellectual property rules that would undermine access to generic medicines.



Regular check-up session for HIV positive patients at Muse clinic in Myanmar.

* A compulsory licence (CL) is an effective option for increasing access to ARVs and other medicines in countries where they are patented. It is a legal mechanism to allow producers other than the originator company to make the drug or to import generic versions into a given country.

STOCKOUTS

For years, many countries have faced shortages and stockouts of essential medicines. Stockouts can be caused by logistical and administrative challenges in procurement, supply chain management, or 'last mile delivery', and by medicines having only a single source (which may lead to shortages: these are generally those under patent, without compulsory or voluntary licences that allow generic manufacturers to supply them).

Because of stockouts, people may receive smaller amounts of the medicine they need, which means extra time-consuming trips to the clinic. They may also be switched to different, less optimal doses or regimens, or be told to buy the medicines they need from the private market with the promise of reimbursement (which is usually not fulfilled), or go without medicine altogether - which can lead to drug resistance and illness.

As countries upgrade their protocols to reflect WHO's new ARV guidelines, governments should make plans for treatment transitions, ensure appropriate buffer stocks and give clear clinical guidance on making switches correctly.

Generics manufacturers must work quickly to avoid shortages and stockouts, using information about current and pipeline ARVs, dose optimisation, changes in treatment guidelines and eligibility, national and global targets for treatment scale-up, and HIV epidemiology to anticipate the quantity of API and final product needed to ensure sufficient availability, while achieving economies of scale.

In South Africa, the Stop Stockouts Project has empowered patients and pushed for accountability in the supply of medicines. The Project receives and publishes daily reports about drug stockouts from people living with HIV and health care workers, conducts comprehensive national surveys to monitor the locations and extent of stockouts, and works with National and Provincial Departments of Health to identify and implement solutions.[61]

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In South Africa, the Stop Stockouts Project – a consortium bringing together six civil society organisations – is pushing for more accountability on stockouts of medicines that impact on people's access to regular treatment.

MARKET SHAPING INSTITUTIONS – WHAT NEEDS TO HAPPEN

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), UNITAID and the Medicines Patent Pool (MPP) have played a central role in the provision of affordable ARVs around the world, including use of quality-assured generic drugs by the GFATM, PEPFAR and other funders.

The GFATM's market-shaping actions go beyond its ability to provide treatment for millions of people, and have an important impact on worldwide ARV access.

After years of contributing towards collective efforts to reduce medicine prices, the scope and remit of the GFATM is increasingly less ambitious and potentially counter-productive. Progress has stalled, especially for middle-income countries, where pharmaceutical corporations seek to charge high prices. Some of these countries have a high disease burden, limited ability to pay for ARVs, and decreasing support from the GFATM and other donors. The GFATM may not be able to guarantee that these countries will be able to access the lowest prices for new medicines, including those under patent, and it may even facilitate problematic tiered pricing strategies used by drug companies in lieu of promoting robust generic competition.

There are clear warning signs that the GFATM is unwilling or unable to defend generic competition for the countries it supports. The GFATM did not signal support for the LDC extension, and has been silent about the Trans-Pacific Partnership trade agreement. It has not explicitly supported the use of TRIPS flexibilities, although this principle has been endorsed since the GFATM started. Instead, the GFATM has been championing an 'e-marketplace' (currently known as wambo.org) to make procurement more efficient. But the e-marketplace is not expected to overcome any access barriers to affordable medicines.

Recent GFATM correspondence indicates that it may seek to optimise tiered pricing policies from drug companies, instead of overcoming commercial pricing strategies. The e-marketplace has been recently criticised by the GFATM's Office of the Inspector General for failing to implement competitive bidding processes for services related to the website.[62]

At best, if the e-marketplace can overcome the challenges it is facing, it could provide minimal technical fixes as to how governments purchase medicines, without dealing with the underlying barriers that make them unaffordable in the first place. At worst, prices offered under the e-marketplace will be insulated from the demands of government and civil society if such products remain unaffordable.

UPDATE ON THE MEDICINES PATENT POOL'S NEW LICENCES

The MPP voluntary licences (VLs) offer some countries the opportunity to gain access to affordable generic versions of new ARVs, although many middle-income and upper-middle-income countries, such as China and Brazil, continue to be left out of these VLs and are therefore prevented from buying the generic drugs produced through manufacturers based in their countries.

On one hand, the MPP has added new VLs, and increased the geographic scope or added new formulations to other licences. In 2014, the MPP announced a new agreement with AbbVie, for two specific paediatric formulations of LPV/r covering 102 low- and middle-income countries.[63]

In late 2015, a separate agreement was signed between MPP and AbbVie on the adult formulation of LPV/r that only covers African countries.[64]

The VL for tenofovir now includes tenofovir alafenamide (TAF) and has an expanded geographic scope that allows generic producers from South Africa and China to join. The VL for elvitegravir (EVT) was amended to include production in China and South Africa, provided that products are made from Gilead-licenced producers of active pharmaceutical ingredients (API).

In March 2016, GlaxoSmithKline (with ViiV) announced that it would increase the geographic scope of its voluntary licensing agreements to include all lower-middle-income countries. The MPP's VL for dolutegravir (DTG) has been expanded to include Armenia, Moldova, Morocco, Ukraine and 14 other low- and middle-income countries. Although this is a welcome first step, excluded upper-middle-income countries will still be forced into tiered pricing schemes, and price-lowering competition will be prevented.

Some MPP licences have been disappointing. AbbVie's new MPP adult licence for LPV/r has a limited geographic scope, and may force specific generics companies that sign the licence agreement to forego the right to supply specific countries that they currently have the right to supply. Furthermore, a new MPP licence with Bristol-Myers Squibb (BMS) for daclatasvir, a hepatitis C medicine, introduces a worrying precedent: it allows BMS to sign sub-licence agreements with generics companies together with the MPP (the normal practice is to not allow branded companies to be involved in signing a sub-licence agreement). MSF is concerned that such a practice could allow branded companies to influence the practices of generics companies, including for unrelated products, and undermine the neutrality of the MPP in managing the sub-licence agreements.

CONCLUSION

The global response to HIV/AIDS has reached a turning point. Ensuring sustainable access to affordable generic ARVs will save millions of lives. Scaling up to 90-90-90 is projected to save over 1.1 million lives and prevent 873,000 new HIV infections in the next five years; keeping up the pace for 10 years will save more than 2.4 million lives (including the mothers of 1.7 million children), and prevent over 2 million new infections.[65]

To accomplish this, governments must commit to scaling-up, optimising and maintaining access to affordable generic ARVs in the long run, as HIV is a disease that requires people to have constant access to a range of treatment options. This will require governments to use TRIPS flexibilities, reform patent laws, and reject harmful TRIPS-plus provisions proposed in various FTA negotiations.

Market-shaping institutions must keep their focus on securing and ensuring a sustainable supply of diagnostics and adult and paediatric ARVs in low- and middle-income countries. The pharmaceutical industry should commit to registering ARVs in all countries, and expanding the scope of their voluntary licensing agreements to include all low- and middle-income countries.

All governments and donors must do their part to accelerate the global HIV response and meet the challenge of the 90-90-90 goals, including fully implementing the latest WHO guidelines, putting in place effective policies at the national level, and ensuring all people living with HIV have access to the most effective drugs, diagnostics and models of care.

METHODOLOGY

Questionnaires were sent to both originator and generics 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 April 2016.

All originator companies marketing ARVs were included in the survey, but the list of generics producers is by no means exhaustive. Only generics companies that have at least one ARV that is quality-assured by WHO Prequalification Programme or US Food and Drug Administration (FDA) on the date of requesting price information were included in this publication. Initial questionnaires were sent to companies in February 2016.

Some important preliminary remarks on the data presented in this report:

- The information on prices given in this publication only relates to ARVs. It does not include other costs linked to antiretroviral treatment, such as diagnosis, monitoring or treatment of opportunistic infections.
- The manufacturers provide the prices listed in this publication. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower as a result of effective procurement procedures or after negotiations. Therefore, the document should not be viewed as a manufacturer's price list.
- Companies use different trade terms (known as incoterms). These incoterms outline the responsibilities of the manufacturer and purchasers with regard to transport, international freight and insurance costs. Additional information and definitions of incoterms can be found in the Abbreviations section at the end of this guide. The incoterms of the prices provided by the companies are reported in Annex 2.
- Originator and some generics companies have different eligibility criteria for differential pricing for countries and entities, meaning not all countries and entities can access the price that is mentioned in this report. The different categories of prices are detailed on the drug profile pages. More detailed information on the different eligibility criteria is provided in Annex 2.
- Information on patents is only indicative and should be checked with national authorities. It should in no way form the basis of a procurement decision.
- As the information on the WHO Prequalification and the US FDA lists are updated regularly, the lists should be consulted for up-to-date information regarding quality.

HOW TO READ THE DRUG PROFILES

GENERAL INFORMATION

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

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

PRICE

All prices are quoted in United States Dollars (US$). Currency conversions were made on the day the price information was received using the currency converter site **www.oanda.com**. Prices are rounded up to the third decimal for unit price and to the nearest whole number for price per person per year (PPPY). The annual cost of treatment PPPY has been calculated according to the WHO dosing schedules, multiplying the unit price (one tablet, capsule or millilitre) by the number of units required for the daily dose, and by 365. The price of the smallest unit is included in brackets.

PAEDIATRICS

Within the tables, paediatric formulations are shaded in order to allow an easier distinction between adults and paediatric formulations. For paediatric treatments, prices are calculated for a 10kg child, using recommended dosing based on the 10kg to 10.9kg weight band as it appears in the WHO paediatric antiretroviral (ARV) treatment guidelines. This is an estimate, as the weight of a child increases during any given year. When it was not possible to calculate the dose for a 10kg child, only the unit price is indicated.

CATEGORIES 1 AND 2 – ACCESS TO PRICE DISCOUNTS

Each originator company applies different eligibility criteria to determine who can access its discounted prices on ARVs. This means that a country that is eligible for a price discount from one company may be excluded from the list of eligible countries by another company. When companies provide two different tiers of discount, the countries eligible for the lowest price are grouped as 'category 1' and countries eligible for a discounted price that is not the lowest price are grouped as 'category 2'. To know whether a country is eligible for a discounted price offered by a given company, or to find out in which category a given country is placed by different companies, please refer to Annex 2.

QUALITY

Products quality-assured by WHO Prequalification Programme or US FDA (as of May 2016) are in **bold** in the tables of drug prices. Readers and purchasers wishing to obtain more information about the quality of ARVs are encouraged to consult the WHO Prequalification Programme website and the US FDA website for approved and tentatively approved ARVs, as these lists are updated regularly.

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

This chart shows the price evolution over time, for both originator and generic products, as quoted to MSF for the purpose of this document. The graph shows the lowest-priced generic product which is quality-assured by WHO Prequalification Programme or US FDA.

SPOTLIGHT ON ACCESS ISSUES

The most salient issues related to access to each product are summarised here. The focus is on the availability of products, their affordability and their adaptability for the developing world. Additional sections have been included to discuss and highlight specific issues with regard to WHO guidelines, paediatrics and patents.

ABACAVIR (ABC)

GENERAL INFORMATION

- **Therapeutic class:** Nucleoside reverse transcriptase inhibitor (NRTI).
- **2016 WHO Guidelines:** ABC is recommended for infants and children under 10 years of age as a preferred first-line NRTI, and for second-line treatment if a thymidine analogue was used in first-line treatment. In adolescents, ABC is recommended as an alternative first-line ARV. For adults, other treatment options are preferred for first-line; ABC is part of second- or third-line regimens.
- Originator company and product brand name: GlaxoSmithKline (GSK); Ziagen. In April 2009, Pfizer and GSK announced the creation of ViiV Healthcare, a joint venture focusing solely on research and development and commercialisation of HIV medicines.
- First approved by US Food and Drug Administration (FDA): December 1998.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults and the 5th edition for children.
- World sales of originator product: 2009: US$160 million; 2008: $175 million; 2007: $215 million; 2006: $230 million; 2005: $268 million; 2004: $290 million. After 2010, sales were not reported in the company's annual report.

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products that are quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	ViiV	Aspen	Aurobindo	Cipla	Hetero
ABC 20mg/ml oral solution (paediatrics)	12ml	**289 (0.066)**	249 (0.057)	**228 (0.052)**		**123 (0.028)**
ABC 60mg tablet (paediatrics)	4				**97 (0.067)**	

SPOTLIGHT ON ACCESS ISSUES

ABC is crucial for people who cannot tolerate zidovudine or tenofovir. For paediatric treatment, ABC is as part of first-line regimens for infants and children up to 10 years of age.

PAEDIATRICS

The 2016 WHO guidelines recommend ART initiation for all children who are less than a year old to 10 years old. The ABC/3TC scored FDC tablet is included in the 2016 Inter-Agency Task Teams on Children and HIV and AIDS (IATT) optimal paediatric ARV formulary.[1]

PATENTS

GSK's basic patent on ABC expired in 2010 in most countries, including middle-income countries such as China[2,3] and Ukraine,[3] and high-income countries such as the United States. GSK applied for secondary patents to extend its patent monopoly, including one on the hemisulfate salt of ABC, filed in 1998.[4]

India: generic production and supply protected

In India, generic production and capacity to supply ABC are protected, thanks to a number of safeguards available in its patent law. GSK could not apply for the basic patent on ABC in India, as India did not grant product patents on pharmaceuticals prior to the full implementation of the TRIPS Agreement.

GSK withdrew its secondary patent application (on the hemisulphate salt) in India in 2007, after the Initiative for Medicines, Access and Knowledge (I-MAK) helped the Indian Network of Positive People (INP+) file an opposition against the application.[5]

Remaining challenges in other countries due to patent barriers

Today, ABC for adults and paediatric versions of ABC/3TC are produced by Indian generics manufacturers and available for export to developing countries, although intellectual property (IP) barriers may prevent some of these countries from importing more affordable generic versions of the adult formulation. For instance, the secondary patent on the ABC hemisulphate salt is being enforced by GSK in China, Malaysia, Ukraine and other countries, thereby posing a barrier until 2018.[3]

In September 2012, the Indonesian government issued compulsory licences (CLs) for several key ARVs, including ABC. The CL will last until May 2018, when the ABC patent expires.[6]

In August 2012, GSK filed a claim to stop the supply and procurement of generic ABC, using an infringement of the hemisulfate salt patent as a threat against four Ukrainian companies and distributors that submitted bids to supply the adult formulation of ABC to the Ukrainian Ministry of Health. GSK also filed for an injunction to prohibit these companies from selling and importing generic ABC from Cipla and Mylan, which was granted in August 2012. GSK's patent infringement claim is being considered by the Kiev commercial court.[7] This litigation has had a chilling effect on suppliers of the generic version of the drug in Ukraine, who are no longer bidding to sell the drug to the Ministry of Health. Ironically, GSK has not been able to use the evergreening hemisulphate salt patent to block generics from the US market, where a number of Indian and Canadian generics are registered.[8]

ViiV also holds patents on different ABC-containing combinations in high-income and many middle-income countries; these can block access to generic versions. For instance, in the United States, ViiV's combination patent on the dual combination of lamivudine and abacavir (3TC/ABC), and a triple combination of lamivudine, abacavir and zidovudine (3TC/ABC/ZDV) was upheld by a District Court after Teva challenged it.[9,10] But the court also ruled that Teva's generic product did not infringe on ViiV's patented product.[9,10] The combination patent of abacavir/doultegravir/lamivudine (ABC/DTG/3TC) has been filed in a number of developing countries such as Brazil, China, Indonesia and countries of the African Regional Intellectual Property Office (ARIPO),[3] and has been granted in countries like Colombia and Ukraine.[3] GSK also holds patents on fixed-dose combinations of ABC with 3TC or emtricitabine (FTC), and with AZT in China, Russia, ARIPO and African Intellectual Property Organization (OAPI) countries.[3] This may hinder access to generic versions of this combination, especially in countries that were excluded from the voluntary licence (VL) signed between ViiV and the Medicines Patent Pool (MPP) in 2013.[11]

In November 2012, Ecuador issued a compulsory licence on ABC/3TC. The licence was issued to Ecuadorean manufacturer Acroxmax, in a bid to reduce the price by 75%.[12]

MPP licence: limited effects

In February 2013, the MPP and ViiV announced a VL agreement for paediatric ABC in 118 countries.[13] Many high-burden, middle-income countries, including Brazil, China, Mexico, Peru, Russia, Uruguay, Ukraine and Venezuela are excluded from the licence agreement. In many of these countries, the secondary patents listed in the licence will not expire until after 2018.[3]

The MPP and ViiV also entered into a separate, non-binding Memorandum of Understanding,[14] which promises collaboration on paediatric licencing of pipeline ARVs, development of novel combination paediatric formulations, and availability of novel paediatric formulations outside of the licenced territories.

GSK: recent statement on relaxing patents in developing countries

In March 2016, GSK released a statement[15] on its future patenting policy in developing countries, including a waiver on submitting patent applications on new drugs in Least-Developed Countries (LDCs). LDCs already benefit from a waiver extension until 2033 from implementing TRIPS obligations, including pharmaceutical patents. GSK's waiver includes low-income countries, but a number of generics-producing middle-income countries are excluded from it, including Brazil and China.

While GSK's announcement recognises "that improving access around the world requires a flexible and multi-faceted approach to intellectual property (IP)"[15], its lawsuit in Ukraine and the limitations of its MPP VL for ABC show that the company does not address the access barriers to ABC that many high-burden, middle-income countries are facing. GSK still enjoys a monopoly in many jurisdictions for ABC, although it was invented in the 1980s; this highlights the dangers of evergreening claims being granted.

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ATAZANAVIR (ATV)

GENERAL INFORMATION

- **Therapeutic class:** Protease inhibitor (PI). ATV should be boosted, either with ritonavir (RTV/r) or cobicistat (COBI).
- **2016 WHO Guidelines:** Boosted ATV (ATV/r) is one of two preferred second-line treatment options for adolescents and adults, including pregnant and breastfeeding women. ATV/r is an alternative second-line ARV for children over three months of age who are failing NNRTI-based regimens.
- Originator company and product brand name: Bristol-Myers Squibb (BMS); Reyataz.
- First approved by US Food and Drug Administration (FDA): June 2003.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults and the 5th edition for children.
- World sales of originator product: 2015: US$1.139 billion; 2014: $1.362 billion; 2013: $1.551 billion; 2012: $1.5 billion; 2011: $1.5 billion; 2010: $1.5 billion; 2009: $1.4 billion; 2008: $1.3 billion; 2007: $1.1 billion; 2006: $931 million; 2005: $696 million; 2004: $369 million; 2003: $81 million.[1]

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.
There are still only three WHO prequalified (WHO PQ) / stringent regulatory authority-approved sources for the generic 300mg capsules, and two sources for each of the other strengths.

	Daily Dose	Bristol-Myers Squibb		Aspen	Cipla	Emcure
		Category 1 countries	Category 2 countries			
ATV 100mg capsule	xx*					**(0.267)**
ATV 150mg capsule	2*	**412 (0.564)**	**412 (0.564)**	380 (0.520)		**207 (0.283)**
ATV 200mg capsule	xx*	**(0.677)**	**(0.677)**	(0.670)		**(0.433)**
ATV 300mg capsule	1*				170 (0.467)	**219 (0.600)**

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

Continued overleaf

SPOTLIGHT ON ACCESS ISSUES

ATV/r cannot be used with rifampicin-based TB treatment, due to drug interactions.

Please refer to the ATV/r drug profile for further information on this combination.

PAEDIATRICS

For children between 6 and 10 years of age, the 2016 WHO Guidelines recommend ATV/r as an alternative second-line treatment, and note that it can be used in children as young as three months. ATV paediatric formulations exist in 100mg, 150mg and 200mg capsules, with one generics company providing prices for all three WHO PQ-approved versions. There is a 50mg/sachet oral powder available from the originator, although it is not widely available or used in developing countries.

PATENTS

Novartis filed for the basic patent on ATV in April 1997; it is expected to expire in April 2017 in most countries.[2] BMS is manufacturing ATV under licence from Novartis. BMS also applied for secondary patents on the crystalline bisulfate salt of ATV in December 1998[3] and on the process for preparing the bisulfate salt and novel forms in 2005,[4] which, if granted, would only expire in 2018 and 2025, respectively.

In many developing countries with the capacity to produce generic pharmaceuticals (including Brazil, China and India), Novartis and BMS have filed patent applications related to the ATV compound,[5] the bisulphate salt,[3] and the best route for making ATV.[6] Some of these patents have been granted in Brazil and China.[7]

Patent oppositions in India leading to access

In India, the base compound patent application on ATV has been challenged by a pre-grant opposition filed by civil society, on the grounds of lack of novelty.[8] The patent application has since been abandoned,[9] but Novartis has filed divisional patent applications.[10] Generics producers such as Matrix and civil society organisations have subsequently filed a number of pre-grant oppositions challenging these divisional patent applications,[11,12] and the cases remain ongoing. In addition, a patent application was filed by BMS in 2006, covering the most efficient route of manufacturing ATV and its bisulphate salt.[13] Subsequent pre-grant oppositions have been filed by generics producers,[14] including an opposition filed by Cipla on a divisional patent application of this application.[15] The patent office subsequently rejected the application.[16] A divisional patent application on this patent has also been opposed by Cipla and has been subsequently rejected by the India patent office.[17]

Voluntary licence and the impact on access

BMS has signed a number of voluntary licence agreements on ATV. For more detailed analysis and discussions on the impact of the agreements, please refer to MSF's report, *Untangling the Web of Antiretroviral Price Reductions* (16th edition).

In October 2012, the Brazilian Ministry of Health approved a licensing agreement between Farmanguinhos and BMS for Brazilian Patent No PI 9701877-5 (WO9740029) - which expires in July 2017 - enabling technology transfer and generic production of ATV. Under the terms of the agreement, the technology transfer would be finished by 2017 and the Ministry of Health's needs for ATV could start to be supplied by Farmanguinhos. However, many delays affected the project, and the registration of the generic version that was originally expected in 2012 did not occur until 2014.[18] This delay could mean that Brazil will be obliged to supply part of its demand from BMS, even after the patent expires. In November 2015, GTPI, a civil society coalition, filed a patent opposition[19] to avoid the grant of a patent (PI0509595-6) that can extend the BMS monopoly until 2024. Brazil currently pays $496.40 PPPY for ATV,[20] and is forbidden by the licence to produce ATV in newer formulations and combinations, such as ATV/r.

On 11 December 2013, the Medicines Patent Pool (MPP) announced a new licencing agreement with BMS for atazanavir. This licence contains territorial coverage of 110 countries, and its 'expanded' territorial coverage could be increased to include countries where patents either do not exist or are not enforced, and countries where compulsory licences are issued.[21] However, a number of middle-income countries (such as Brazil, China, Thailand, Ukraine and Venezuela) are excluded from the licence, as well as Russia. In addition, the terms and conditions under previous bilateral voluntary licences and technology transfer agreements between generics companies and BMS may significantly restrict the actual ability for those companies to operate under this MPP licence, especially if the previous licences and agreements cannot be replaced by the MPP licence agreement. In December 2013, Brazilian civil society groups announced their dissatisfaction with the Brazilian government's voluntary licencing strategy for ATV after detailed terms and condition of the MPP licence were made public.

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ATAZANAVIR/ RITONAVIR (ATV/R)

GENERAL INFORMATION

- **Therapeutic class:** Ritonavir (RTV/r)-boosted protease inhibitor (PI) in a fixed-dose combination (FDC).
- **2016 WHO Guidelines:** Boosted ATV is one of two preferred second-line treatment options for adolescents and adults, including pregnant and breastfeeding women. ATV/r is an alternative second-line ARV for children over three months of age who are failing NNRTI-based regimens.
- Originator company and product brand name: No originator product exists.
- First approved by US Food and Drug Administration (FDA): Mylan's product was approved under the tentative approval scheme in November 2011.
- WHO Model List of Essential Medicines (EML): ATV and RTV are included as stand-alone products in the 19th edition for adults, and included as stand-alone products in the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of originator product: not applicable.

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Cipla	Emcure	Hetero
ATV/r 300/100mg tablet	1	213 (0.583)	**213 (0.583)**	219 (0.600)

The cost of the FDC is much less than the individual components (ATV/r: $213 PPPY versus ATV 300mg + RTV 100mg: $302 PPPY).

SPOTLIGHT ON ACCESS ISSUES

Two WHO-prequalified FDCs of ATV/r are now available, with others in the pipeline. This will help to improve the supply stability of second-line ARVs. A stable supply chain is relevant for second-line ARVs, given the past shortages experienced with lopinavir/ritonavir (LPV/r). ATV/r should be considered by countries who continue to list only LPV/r for second-line, since it is a WHO- preferred second-line alternative.

ATV/r is well tolerated and convenient: it is once-daily, and the pill burden has been reduced by the generic, heat-stable, quality-assured FDC.

ATV/r should not be used by people who are taking rifampicin-based TB treatment, due to drug interactions.

PAEDIATRICS

For children between 6 and 10 years of age, the 2016 WHO Guidelines recommend ATV/r as an alternative second-line antiretroviral, but note that it can be used in children as young as three months (with consideration of the limited availability of suitable formulations, such as an FDC). A paediatric FDC does not exist, but has been included in the 2016 WHO prequalification Expression of Interest, to stimulate interest in this product for second-line treatment in children.

PATENTS

There are patent applications by BMS on the specific compositions of ATV with other ARVs, including RTV. [1,2,3,4]

Some of these applications have been abandoned or withdrawn in India,[5,6] and others are pending.[7] These applications have been withdrawn in China.[8] Where granted, the patents on composition of ATV and RTV might have impact on access to generic versions of the combinations. Individual patents on ATV (see the ATV drug profile) and on RTV (see the LPV/r profile for information about RTV), would also have an effect on production of generic versions of this combination.

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DARUNAVIR (DRV)

GENERAL INFORMATION

- **Therapeutic class:** Protease inhibitor (PI). DRV should always be boosted, either with ritonavir (RTV/r) or cobicistat (COBI).
- **2016 WHO Guidelines:** Ritonavir-boosted, heat-stable DRV is an alternative option for second-line treatment, and remains an option for third-line treatment.
- Originator company and product brand name: Janssen; Prezista. Janssen (formerly known as Tibotec) is a subsidiary of Johnson & Johnson.
- First approved by the US Food and Drug Administration (FDA): June 2006.
- WHO Model List of Essential Medicines (EML): Not included in the 19th edition for adults or the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of originator product: 2015 (includes boosted co-forumation): US$1.81 billion; 2014: $1.83billion; 2013: $1.67 billion; 2012: $1.4 billion; 2011: $1.2 billion; 2010: more than $1 billion reported.[1]

PRICE INFORMATION

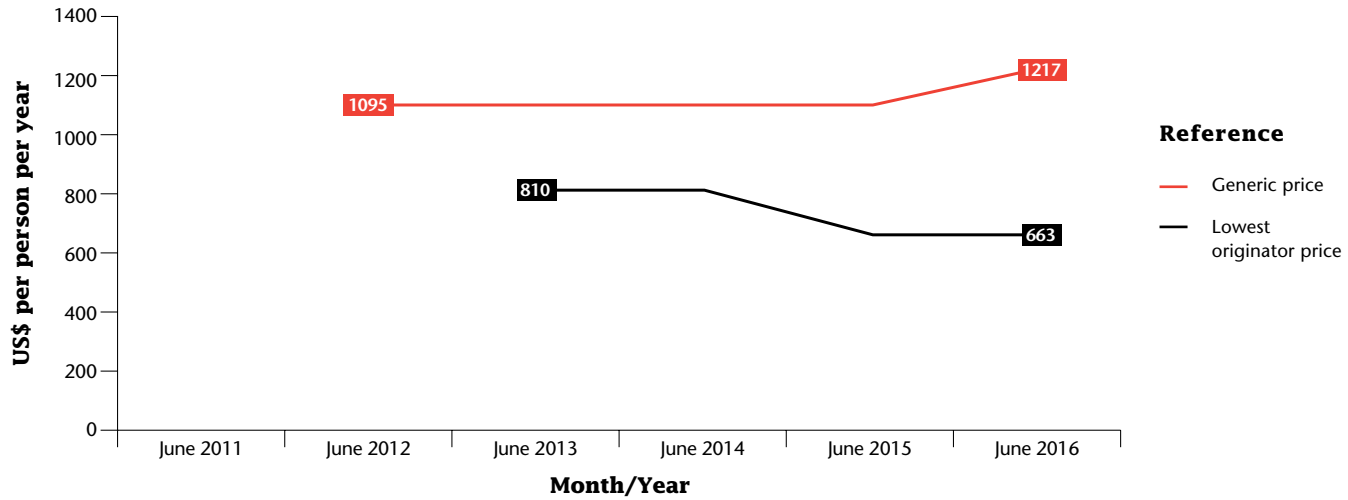
Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Janssen	Aspen	Hetero
DRV 75mg tablet	xx	**(0.114)**		
DRV 150mg tablet	xx	**(0.227)**		
DRV 400mg tablet	2*	**438 (0.600)**		**973 (1.333)**
DRV 600mg tablet	2**	**663 (0.908)**	**658 (0.901)**	**1,217 (1.667)**

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

The price of generic DRV 600mg is almost twice as high as Janssen's access price ($1,217 PPPY from Hetero vs. $663 PPPY from Janssen). Despite having multiple generic versions – plus the originator darunavir formulations that are WHO-prequalified and/or US FDA-approved – the price of DRV has not decreased, due to lack of commercialisation of DRV by some generics companies (which is likely related to small volume markets). DRV/r is likely to be used in only for third-line treatment until the price comes down. A search of the Global Fund Price and Quality Reporting database shows that from 2013-2015, Janssen supplied the majority of the DRV procured.

DRV 600MG TABLET



SPOTLIGHT ON ACCESS ISSUES

WHO guidelines recommend darunavir (DRV/r) as an alternative second-line treatment option. DRV/r is better tolerated than the other second-line options, ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted lopinavir (LPV/r),[2,3,4,5,6] but it is an alternative regimen because of its high price and the current lack of a heat-stable DRV/r fixed-dose combination (FDC). Generic producers are working on a heat-stable DRV/r (400mg/50mg) FDC.[7]

DRV/r cannot be used during rifampicin-based TB treatment due to a drug interaction. However, modelling data suggest that increasing the dose of DRV/r (to 800mg/100mg twice-daily, or 1200mg/150mg twice-daily) might make it possible to co-administer it with rifampicin, pending results from a clinical trial.[8]

PAEDIATRICS

The 2016 WHO guidelines include DRV/r as an alternative second-line option for children who are three to ten years of age. (It is not recommended for use in children who are under three years of age.) Paediatric formulations of 75mg and 150mg tablets and an 100mg/ml oral solution are available from the originator; there are 2 suppliers for generic 75mg tablets, and 3 suppliers for generic 150mg tablets. Janssen has started a donation programme for qualifying countries (so far, Kenya, Lesotho, Swaziland and Zambia)[9] – although it does not provide ritonavir. The donation programme may make the low-volume paediatric market even less enticing for generics.

PATENTS

In most countries, the basic patent of DRV expired in 2013.[10,11] But secondary patents on DRV related to key intermediates and combinations with ritonavir (RTV/r) and tenofovir (TDF) will expire in 2025 in countries where they have been granted.[11]

Patent oppositions in India

The basic patent related to DRV[12] could not be applied for in India, because it did not grant product patents on pharmaceuticals in 1994. After the implementation of the TRIPS agreement in 2005, which obliged India to accept product patent applications, Janssen (Johnson & Johnson) applied for several secondary patents in India related to DRV.[13] Pre-grant oppositions were filed against all of these applications; several were rejected by the Indian patent office.[11,14,15,16,17] The patent application on the combination of DRV with TDF was withdrawn.[11,18]

A divisional patent application[19] concerning the combination of DRV with RTV has been abandoned by Janssen (J&J) after a pre-grant opposition by a generics manufacturer.[20] Other patent applications concerning RTV have been either rejected or abandoned after patent oppositions were filed by civil society organisations in India.[21]

Access challenges in other developing countries

In China, Janssen was granted patents related to racemic and pseudo-polymorphic forms of DRV,[11,22] and the same patent has been granted in South Africa.[11,23] The patent concerning the combination of DRV and RTV, and the combination of DRV, RTV and TDF has been withdrawn or lapsed in China, Brazil and South Africa, but it has been granted in other developing countries such as Mexico, Philippines and Turkey.[11]

In 2015, Brazil and other Mercosur countries engaged in joint negotiations for HIV drugs. One of their achievements was the regional price reduction for the 600mg dose of DRV (to $1.26 per unit or $919.80 PPPY).[24] However, the effects of the negotiation remain uncertain, given that the price Brazil paid in 2016 is still the price that Janssen offered the country before the Mercosur deal ($2.98 per unit or $2175.40 PPPY).[25] Civil society groups have been sending letters to the government, claiming that the price must drop immediately, and that although there are 18 patent applications related to darunavir in Brazil, none of them block the use of generic versions.[26]

Voluntary licence

In September 2010, the US National Institutes of Health (NIH) licenced patents on DRV to the Medicines Patent Pool (MPP).[27] The move demonstrated political backing for the MPP, and it was also significant because all developing countries were covered in the geographical scope of the licence. However, the NIH patent will not clear the way for generic versions of DRV in all developing countries, due to additional patents held by Janssen. In December 2011, the company announced its decision not to enter into negotiations to licence its HIV drugs portfolio, including DRV, to the MPP.[28] In doing so, it has effectively made the NIH licence useless for manufacture and export to countries where Janssen holds a patent.

Janssen is, however, engaging in bilateral voluntary licensing with two generics companies – Aspen in South Africa and Emcure in India[29] – but only for packaging and distribution. The terms of the licences are not public.

In June 2011, Janssen announced that it had entered into a licence agreement with Gilead for the development and commercialisation of a new once-daily single tablet fixed-dose combination containing DRV and Gilead's cobicistat, and the agreement was amended in 2014.[30] Subject to regulatory approval, Janssen will be responsible for the formulation, manufacture, registration, distribution and commercialisation of the regimen of DRV/cobicistat combination worldwide.

Continued overleaf ⋯

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DOLUTEGRAVIR (DTG)

GENERAL INFORMATION

- **Therapeutic class:** Integrase inhibitor.
- **2016 WHO Guidelines:** Dolutegravir (DTG) was added as alternative first-line antiretroviral (ARV) option for adults, and for use in salvage treatment. For adolescents over 12 years old, DTG was added as an alternative first-line ARV. Before it can become a WHO-preferred first-line regimen, more data are needed in pregnant and breastfeeding women, and during rifampicin-based TB treatment.
- Originator companies and product brand names: ViiV Healthcare (a Pfizer/GSK partnership founded in 2009 to develop and commercialise HIV medicines) and Shionogi; Tivicay (the DTG fixed-dose combination with abacavir [ABC] and lamivudine [3TC] is Trimeq).
- First approved by US Food and Drug Administration (FDA): For adults and adolescents, in August, 2013. In 2016, this indication was expanded to include dolutegravir for children weighing at least 30kg.[1]
- WHO Model List of Essential Medicines (EML): Not yet included.
- World sales of originator product: In 2014, Shionogi reported global sales of US $372.2 million for dolutegravir singles and $75.2 million for DTG-containing FDCs.[2,3]

PRICE INFORMATION

Prices not available/not quoted; generic versions are not yet available.

Dolutegravir-based treatment could lower the price of ART, since it is effective at only a 50mg dose. Many generics producers have DTG ready, and are working on FDCs, with the first USFDA approval of generic DTG expected in mid-2016. The launch price of Aurobindo's DTG was announced to be approximately on par with EFV 600mg, at $44 per person per year (PPPY).[4] In the meantime, ViiV is providing DTG at access prices that vary, based on volumes and shipping, in all least-developed countries (LDCs), low-income countries, and all sub-Saharan African countries.

SPOTLIGHT ON ACCESS ISSUES

Once-daily DTG has a higher resistance barrier and better tolerability than EFV.[5] Research is needed on DTG dosing[6] and efficacy during pregnancy (and breastfeeding), since women are recommended to increase their intake of calcium and iron, both of which reduce DTG levels.[7] The current recommendation is to double the dose of DTG during rifampicin-based TB treatment,[8] but there is still limited clinical experience to validate this strategy in the context of real-life scale-up.

PAEDIATRICS

The 2016 WHO guidelines include DTG as part of salvage treatment for children. DTG is recommended for children six years and older who weigh ≥30kg.

PATENTS

Japanese company Shionogi and its licencee ViiV Healthcare have filed multiple patents on DTG, covering its main compound, intermediaries and synthetic processes. The base compound patent has been granted or filed in many countries, including Brazil, China, the Eurasian Patent Organization (EAPO), Egypt, India, Indonesia, the African Intellectual Property Organisation (OAPI) and South Africa.[9] The base compound patent will not expire before 2026.[9] Other patents will start expiring in 2029.[9]

India

The patent application for dolutegravir's main compound was filed in India on 10 November 2007 as Indian Application No. 3865/KOLNP/2007. Since 2013, three pre-grant oppositions have been filed in India by civil society organisations and other individuals against the grant of this Indian application[10] (which is equivalent to the international publication number under WIPO PCT, WO2006116764). GSK subsequently narrowed and amended its claims. The matter is still pending.

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The final outcome of the opposition will determine the patentability of dolutegravir's main compound, as well as other patent applications related to ARVs with a similar chemical structure (the application also includes ViiV's new pipeline ARV, cabotegravir, which is being developed both as tablets and in a long-acting injectable formulation). This is because the application concerning DTG's base compound was filed under the so-called 'Markush claim', where millions of possible compounds are included in a single patent application without disclosing which ones will be put into development and production.

A number of evergreening patent applications have been filed in India, including a divisional application 485/KOLNP/2013 concerning the compound of DTG; an application that claims the DTG product, filed as 2071/KOLNP/2008; an application on the crystalline form of DTG and the process for the preparation of DTG, which was filed in 2011 as 1942/KOLNP/2011; an application on the intermediates of DTG, filed as 1971/KOLNP/201; and an application on crystalline intermediate compounds of DTG, filed as 886/CHENP/2013. All of these applications are now pending for examinations in India.

To date, the drug is not available from ViiV in India, as the company has neither applied for registration in the country, nor made DTG available under a 'compassionate use' programme.

MPP licence

On 1 April, 2014 the Medicines Patent Pool (MPP) and ViiV healthcare announced a new collaboration, comprised of two voluntary licences (VLs) on patents related to a paediatric formulation of DTG,[11] and the adult formulation of DTG, which includes the flexibility to develop FDCs with abacavir (ABC) and other compounds if there are no patents in force.[9] The licence on the adult formulation was amended in April 2016 to include more low- and middle-income countries.*[12]

The licence adopted a hybrid royalty structure. The paediatric licence agreement is royalty-free in 121 countries where the product is sold. The adult licence, after an amendment, includes 82 low-income countries (royalty-free) and 10 middle-income countries (Armenia, Egypt, India, Indonesia, Moldova, Morocco, Philippines, Turkmenistan, Vietnam and Ukraine), with a sliding royalty scheme, based on per-capita income;[11] it excludes certain middle-income countries, such as Brazil, China, Malaysia, Russia and Thailand.

The licence adapted a market segmentation approach. Both public and private markets are included in the 82 royalty-free countries for the adult formulation, but in the 10 middle-income countries where there is a tiered royalty rate, ViiV only allows sales to the public sector market (defined to include non-profit organisations and public funding mechanisms that ViiV has authorised). In this licence, ViiV's public vs. private market division creates practical barriers for access in countries such as India, where the national treatment programme is still in the process of revising guidelines to include DTG, and generic versions are not available in the private market for people who may need immediate access.[13]

For countries outside of the licensed territories where there are currently no blocking patents on DTG (including Argentina and Venezuela), access to generic DTG would depend on a number of other factors. These include the future status of any relevant patent filing; the willingness of generics companies to supply companies outside the territories of the VL; regulatory barriers such as data exclusivity or the requirement of originator registration; and the actual process and speed of registration of generic versions in these countries.

Although developing an ABC/DTG FDC has been covered by the adult licence, the licence would have an impact on development of an FDC that contains active ingredients other than ABC. For instance, ViiV holds a patent on the combination of ABC/3TC/DTG,[14] which will not expire until 2031. The patent has been filed widely in developing countries and has already been granted in some countries, such as South Africa and Ukraine.[9,15] Developing and importing the combination of ABC/3TC/DTG will be hindered in countries where this patent has been granted. In addition, this patent application has been filed in 20** out of the 82 royalty-free countries, and all of the 10 tiered-royalty countries including India; the patent has been granted in Ukraine. If the combination patent is granted in these countries, it could block the development of, and access to, a more affordable generic version of this FDC.

For countries that are not covered by the licence and where the DTG patent is not yet granted, the ABC/3TC/DTG combination patent application has been filed in seven countries (Albania, Bosnia, Colombia, Dominican Republic, Montenegro, Peru and Thailand). If the patent is granted - even where an active patent on DTG is not issued - these countries would be unable to secure a supply of a generic FDC that contains ABC/3TC/DTG. In addition, for the Dominican Republic, Peru and Thailand, where there is also an ABC patent in place, access to generic ABC/3TC/DTG will not be possible if this combination patent is granted.[9]

*The 14 new countries included in the amendment are: Bolivia, El Salvador, Georgia, Guatemala, Guyana, Honduras, Kosovo, Micronesia, Nicaragua, Pakistan, Papua New Guinea, Syria, Uzbekistan, and West Bank of Gaza; the additional tiered royalty countries are: Armenia, Moldova, Morocco, and Ukraine.

**The 20 countries are: Botswana, Gabon, Gambia, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, São Tomé and Príncipe, Sierra Leone, Somalia, Sudan, Swaziland, Tajikistan, Tanzania, Uganda, Zambia and Zimbabwe.

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ETRAVIRINE (ETV)

GENERAL INFORMATION

- **Therapeutic class:** Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- **2016 WHO Guidelines:** ETV is indicated as an option for third-line treatment regimens.
- Originator company and product brand name: Janssen; Intelence. Janssen (formerly known as Tibotec) is a subsidiary of Johnson & Johnson.
- First approved by the US Food and Drug Administration (FDA): January 2008.
- WHO Model List of Essential Medicines (EML): Not included.
- World sales of originator product: No recent data available; 2012: US$349 million; 2011: $314 million; 2010: $243 million.

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Janssen	Aspen
ETV 25mg tablet	xx	**(0.075)**	
ETV 100mg tablet	4	**438 (0.300)**	**438 (0.300)**

SPOTLIGHT ON ACCESS ISSUES

The WHO guidelines recommend ETV as part of third-line treatment. As of now, there are no generics manufacturers producing quality-assured ETV. Aspen provides Janssen's product in sub-Saharan African countries where it is already registered; otherwise, only Janssen supplies ETV. Pricing was not provided for adult 200mg tablets.

PAEDIATRICS

ETV is approved for ARV-experienced children over the age of six and adolescents. It is available in 25mg and 100mg tablets from the originator. No quality-assured generic formulations exist. ETV is not in the IATT 2016 paediatric formulary optimal or limited use lists, as it is not specifically indicated in the WHO guidelines. Janssen has started a donation program for qualifying countries (so far, Kenya, Lesotho, Swaziland and Zambia),[1] which may make the low-volume paediatric market even less enticing for generics.

PATENTS

The patent on the base compound of ETV has been widely applied for by Janssen in the developing world, including in sub-Saharan Africa. Janssen obtained a patent on the ETV molecule in ARIPO and OAPI countries,[2,3] China,[2,4] and India.[2,5] This patent will not expire before 2019. In India, Janssen has filed additional ever-greening patent applications [6,7] on new forms, which, if granted, will extend its monopoly in India from 2021 to 2027. Janssen also applied for a composition patent on the solid formulation of ETV, which has been granted in a number of developing countries including China, India, Mexico, Russia, South Africa, Ukraine and OAPI countries; it is set to expire in 2020.[2,8]

These patents, if not tackled, could block the development of generic formulations of ETV. In August 2009, Janssen signed a royalty-free, non-exclusive agreement with Aspen for ETV, covering all of sub-Saharan Africa and LDCs.[9] This is not a manufacturing licence; Aspen handles regulatory and distribution activities on ETV under this agreement. The full terms are not public and the geographic scope is limited.

In December 2011, Janssen announced its decision not to enter into negotiations with the Medicines Patent Pool to licence its portfolio of HIV drugs, including ETV.[10] With patent restrictions in place, robust generic competition will not be possible until Janssen is ready to consider open and transparent licensing mechanisms.

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LOPINAVIR/ RITONAVIR (LPV/R)

GENERAL INFORMATION

- **Therapeutic class:** Boosted protease inhibitor (PI) in a fixed-dose combination.
- **2016 WHO Guidelines:** LPV/r is recommended for first-line treatment for children under three years of age, regardless of NNRTI exposure. LPV/r is also indicated as part of second-line treatment for adults, including pregnant and breastfeeding women, and children.
- Originator company and product brand name: Abbott; Kaletra or Aluvia. In 2013, Abbott separated into two companies, Abbott and AbbVie; AbbVie holds the portfolio for most pharmaceuticals, including Kaletra.
- First approved by US Food and Drug Administration (FDA): September 2000 for soft-gel capsules; October 2005 for heat-stable tablets.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults and the 5th edition for children.
- World sales of originator product: 2015: US$700 million; 2014: $870 million; 2013: $962 million; 2012: $733 million; 2011: $1.2 billion; 2010: $1.3 billion; 2009: $1.4 billion; 2008: $1.5 billion; 2007: $1.3 billion; 2004: $897 million; 2003: $754 million; 2002: $551 million; 2001: $292 million.[1]

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.

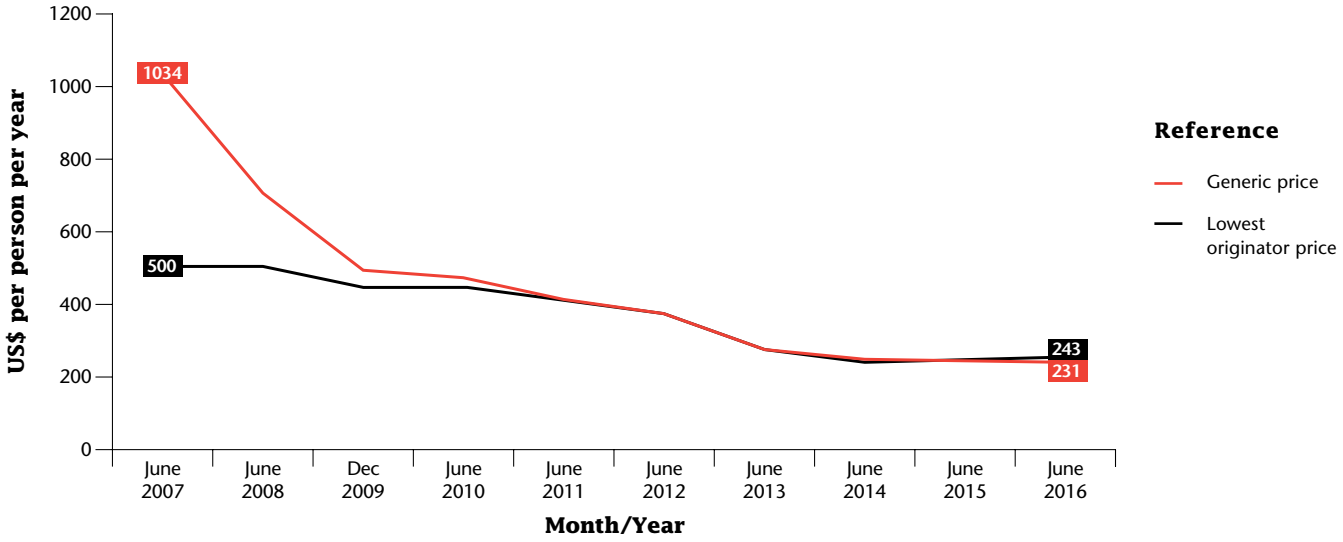
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.

Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	AbbVie		Aurobindo	Cipla	Hetero	Macleods
		Category 1 countries	Category 2 countries				
LPV/r 80/20mg/ml oral solution (paediatrics)	4ml	**150 (0.103)**	**296 (0.203)**				
LPV/r 40/10mg capsule (paediatrics)	xx				**(0.160)**		
LPV/r 100/25mg heat-stable tablet (paediatrics)	3	**108 (0.099)**	**278 (0.254)**	**151 (0.138)**	155 (0.142)		**143 (0.131)**
LPV/r 200/50mg heat-stable tablet	4	**231 (0.158)**	**740 (0.507)**	**243 (0.167)**	**268 (0.183)**	**280 (0.192)**	**293 (0.201)**

Evolution of the lowest price quoted for eligible developing countries:
In 2014, the price of generic LPV/r 200/50mg tablets came down to $243 PPPY, and seems to have stabilized there. The price of originator LPV/r is slightly lower, at $231 PPPY; in South Africa, where AbbVie is the only supplier, the price for LPV/r is lower – as of July 2016, it was $182 PPPY.[2]

LPV/R 200MG/50MG TABLET



SPOTLIGHT ON ACCESS ISSUES

There are four WHO-prequalified suppliers of generic LPV/r tablets for adults (200mg/50mg).

In 2015, despite the number of suppliers in the international market, there was a significant LPV/r stockout across South Africa. MSF reported that 65% of people were sent away without any medicine, while 35% only received a partial supply,[3] leaving them vulnerable to drug resistance and treatment failure. The LVP/r supply is likely to remain unstable, since AbbVie has been undercutting generic competition with slightly lower prices. This has made it difficult for generics to enter the market in countries including South Africa, where Abbvie held the patent for LPV/r until a recent agreement with the Medicines Patent Pool (MPP) in December 2015; Aurobindo, Desano and Emcure have recently signed the VL through the MPP on the adult formulation, and Hetero has signed on the paediatric formulation.[4,5]

PAEDIATRICS

There are currently three WHO-prequalified, approved suppliers of generic LPV/r tablets for children (100mg/25mg). In June 2015, Cipla received FDA approval for a new pellet formulation of LPV/r, but it is not commercially available yet. Cipla is the only WHO prequalified manufacturer of the oral solution, but it is no longer in production, leaving children under three years old with the originator product as their only option until the new pellet formulation becomes available.

LPV/r pellets are a far more favourable formulation than the oral solution, which contains 40% alcohol, tastes very bitter, and requires a cold chain, but the price of the pellets may be a barrier in some countries. LPV/r pellets cost $19.20 for a bottle of 120. For a 10kg child, at a dose of eight capsules per day (which equates to two bottles per month), the price is $460.80 PPPY compared to $150 PPPY for oral solution, or $108 PPPY for paediatric tablets.

Countries are likely to recognise the benefits of LPV/r pellets, especially for younger children. To ensure better access to the LPV/r pellets, Cipla needs to reduce the price so that it is at least on par with the oral solution. Further modification of the pellets to produce a taste-masked formulation is underway, since the bitter taste remains.

PATENTS

Most patents related to ritonavir (RTV/r) also cover LPV/r. Abbott applied for the basic patent related to LPV in 1996.[6] In addition, Abbott applied for patents more specifically related to the LPV/r soft-gel capsules in 1997,[7] which are due to expire in 2017. An application for a patent on the LPV/r heat-stable tablet formulation that is now widely used in developing countries was filed in 2004;[8] it could potentially run until 2024.

Access in Developing Countries

Abbott could not file a patent on the base compound of LPV in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS

Continued overleaf

agreement, such as India. Competition from Indian generics manufacturers has, together with increased global demand, brought down the price of LPV/r in some countries.

However, Abbott applied for several other patents in India, including polymorphic forms of LPV and RTV,[10,11,12] the combination of LPV/r,[13] and the process of making LPV.[14] These patents have all been rejected by the India patent office, or abandoned by Abbott,[9,15,16,17] following a series of pre-grant oppositions filed by civil society organisations or generics producers.[17]

There is another patent application on the solid pharmaceutical dosage (tablet) formulation of RTV.[18] This application is pending. Pre-grant oppositions have been filed by generics producers and the India Network of People Living with HIV/AIDS since 2013.[19] If this patent application is granted, current generic competition on LPV/r could be under threat.

In Thailand, where Abbott holds patents on LPV/r, the drug was costly, so the Ministry of Public Health issued a compulsory licence in January 2007 to import more affordable generic versions of the drug from India.[20] Thailand faced fierce criticism from developed countries and multinational pharmaceutical corporations for the decision. Abbott's response was to withdraw all applications to register its new products in Thailand, including heat-stable LPV/r, which triggered heavy criticism of Abbott from civil society worldwide.[21]

In Brazil, more than 70,000 HIV-positive people use LPV/r. The original patent on the drug is about to expire, but AbbVie, the current patent holder, is using many strategies to extend their monopoly. GTPI, a civil society coalition, filed a patent opposition in 2011[22] to prevent the grant of a patent (PI 0413882-1) that would extend the monopoly from 2016 to 2023. In 2013, the patent application was rejected by ANVISA and later by Instituto Nacional da Propriedade (INPI), Brazil's Institute of Intellectual Property. However, the company has filed multiple appeals, including in the courts, where it managed to obtain decisions that undermine the rejection. GTPI has also filed an amicus curiae brief at the Supreme Court, and a final decision is still pending.[23]

In November 2011, several public health groups – including Public Citizen – launched a global campaign across 12 countries to challenge Abbott's patents on LPV/r, using patent oppositions or requests for compulsory licences. In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including LPV/r. This licence will last until the patent expires in August 2018.[24]

In Ecuador, where a compulsory licence was originally issued on RTV, the government has been evaluating a new licence request regarding the LPV/r patent.[25] However, upon a bilateral free trade agreement signed with the European Union in 2014, several requests for compulsory licences have been withdrawn by Ecuador's public pharmaceutical firm, after four compulsory licences were previously issued on pharmaceuticals in the same year.[26]

MPP licence, including its limitations

In December 2014, AbbVie entered into a licence agreement with the MPP on the paediatric formulations of LPV/r and RTV.[27] The licence is royalty-free and generics manufacturers from any country can join. The AbbVie licence with the MPP covers 102 developing countries, but it excludes a number of countries, including Argentina, Brazil, China and Ukraine. Generic access is possible for excluded countries if patents are not in force – as in India, where the patent was withdrawn – or if the countries use compulsory licensing.

The MPP-AbbVie licence covers both the liquid formulation of LPV/r and the 40mg/10mg pellet formulation[28] that are used for children under three years of age. But the licence does not cover the paediatric 100mg/25mg tablet, which is needed for children over three years of age. This has left a significant gap for all paediatric patients who need the right formulation for effective treatment.

AbbVie's licence has had a chilling effect on registration of the 100mg/25mg paediatric tablet, affecting its availability in countries where Abbott holds a number of patents on lopinavir and ritonavir. Since a double dose of the paediatric tablet could be used by adults, AbbVie's strategy also helps maintain their monopoly on adult formulations.

Moreover, before the full implementation of the licence by generics producers, access to generic versions of the two paediatric formulations of LPV/r remains absent.[29] At the time of going to press in July 2016, only one Indian generics company, Hetero, has signed the sub-licence for the paediatric formulations, but full registration and supply to the market will still take time to be realised.[30]

In December 2015, AbbVie entered into a new licence agreement with the MPP on the adult formulation of LPV/r; it covers all countries in Africa.[31] Due to its defined geographic coverage, people in all countries outside of Africa remain excluded where patents are currently in force, unless other legal and policy measures are used (such as issuing a compulsory licence). For instance, with the compulsory licence on LPV/r, Thailand has secured more affordable generic versions of LPV/r, and can continue to do so from companies that sign the voluntary licence, whilst neighbouring countries such as Malaysia will remain unable to access affordable versions of LPV/r. In July 2016, the MPP announced its newly signed sub-licence agreements with the Chinese generics company Desano, and the Indian generics companies Emcure and Aurobindo for the adult formulation.[4]

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RALTEGRAVIR (RAL)

GENERAL INFORMATION

- **Therapeutic class:** Integrase inhibitor.
- **2016 WHO Guidelines:** RAL is indicated as an alternative option (in combination with LPV/r) for second-line treatment of adults and adolescents, and as part of third-line treatment for adults, pregnant and breastfeeding women and adolescents. It is included as a second-line treatment regimen for infants and children.
- Originator company and product brand name: Merck; Isentress.
- First approved by US Food and Drug Administration (FDA): October 2007.
- WHO Model List of Essential Medicines (EML): Not included.
- World sales of originator product: 2015: US $1.511 billion; 2014: $1.673 billion; 2013: $1.643 billion; 2012: $1.5 billion; 2011: $1.4 billion; 2010: $1.1 billion; 2009: $752 million; 2008: $361 million; 2007: $41 million.[1]

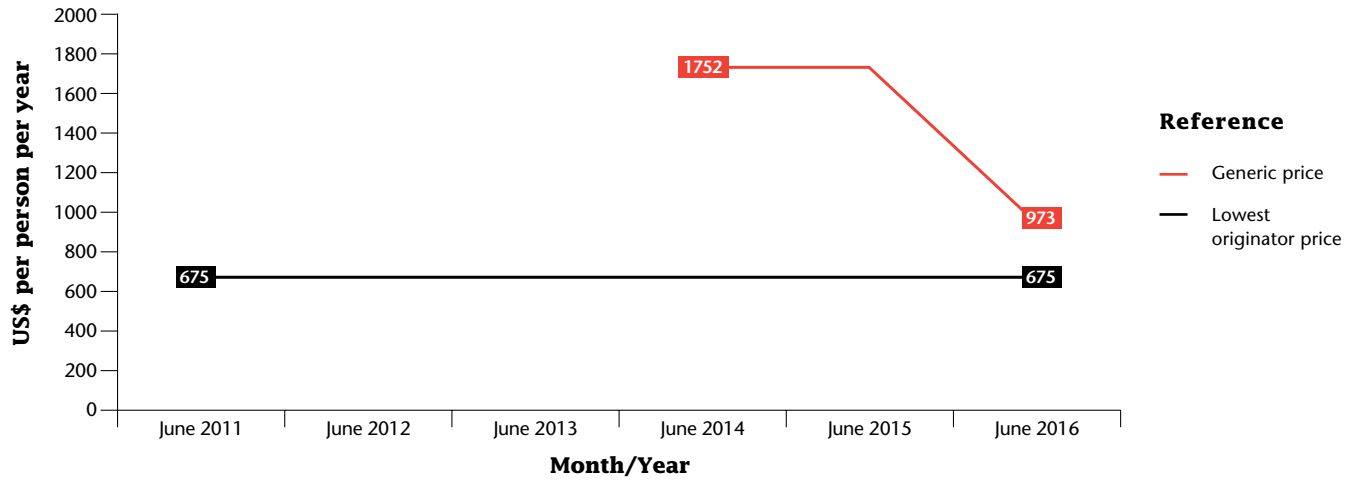
PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Merck		Hetero
		Category 1 countries	Category 2 countries	
RAL 25mg chewable tablet	xx	**(0.300)**	**Case-by-case basis**	
RAL 100mg chewable tablet	xx	**(0.600)**	**Case-by-case basis**	
RAL 400mg tablet	2	**675 (0.925)**	**Case-by-case basis**	**973 (1.333)**

The price quoted for generic RAL is 44% higher than Merck's access price. Until there is further investment in the market by other generics companies to increase competition, the price will likely not improve and access to RAL for second- and third-line treatment will remain out of reach for many.

RAL 400MG TABLET



SPOTLIGHT ON ACCESS ISSUES

RAL is indicated as a second- and third-line treatment option for adults and adolescents. There is one WHO-prequalified supplier of generic RAL, but the generic version of RAL has not been consistently available, so it continues to be supplied by the originator.

PAEDIATRICS

RAL is indicated as a second-line option for children who have failed a lopinavir/ritonavir-based regimen. RAL is available from Merck in 100mg scored chewable tablets, 25mg chewable tablets and 100mg sachet granules. The 25mg and 100mg tablets are approved for children as young as two years (and 10kg). The granule formulation (which is not bioequivalent to the chewable tablets) is indicated for children as young as four weeks (between 3kg and 2kg), but is difficult to use. The RAL 100mg chewable tablets are on the optimal IATT paediatrics formulary list; the 25mg chewable tablets are on the limited use list.[2] There are still no generic formulations of RAL for paediatrics, but two generics companies (Hetero and Lupin) recently signed licenses to start development.[3]

PATENTS

The Institute for Research in Molecular Biology (IRBM), one of Merck's research sites, applied for the patent of the base compound on RAL in October of 2002.[4] This patent is due to expire in 2022. In 2005, Merck and IRBM applied for additional evergreening patents on the potassium salt and film-coated tablet of RAL, which can run up to 2025.[5] These patent applications have been widely filed in developing countries, including some with the capacity to manufacture generic drugs, such as Brazil, China, India and South Africa.[5] In India, IRBM was granted a base patent on RAL in December 2007, which will not expire until 2022.[6] An application on the potassium salt of RAL[5] is also pending for review before the Indian patent office, and a pre-grant opposition was filed in July 2011.[8]

In 2011, Merck signed voluntary licences with the generics companies Emcure, Matrix and Mylan, to supply RAL to 60 sub-Saharan African and low-income countries.[9] Though generic production for export is possible under the licence, the RAL that is locally produced by the licencees cannot be marketed in India, nor is it available for procurement by MSF projects in India.

In February 2014, Indian drug manufacturers Cipla and Merck announced an India-specific partnership under which Cipla will have a non-exclusive licence to market, promote and distribute Merck's RAL under a different brand name.[10] This deal was apparently signed by Merck to counter an ongoing push in India to issue a compulsory licence to lower the price of RAL.[11] The deal between Merck and Cipla is a disappointment, because it does not enable generic competition in India among multiple producers, which could lead to dramatic price reductions.[12]

In 2011, Brazil's Ministry of Health announced the establishment a technology transfer agreement with Merck for RAL, but it did not move forward and the contract was cancelled in 2015.[13] Brazil currently pays US$4.98 per pill for the 400mg version, or $3635.40 PPPY.[14]

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TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

GENERAL INFORMATION

- **Therapeutic class:** One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a fixed-dose combination (FDC).
- **2016 WHO Guidelines:** TDF/3TC is recommended as part of first-line treatment for adults, including pregnant and breastfeeding women, adolescents, and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV). For adolescents who are over 10 years old, TDF/3TC is the preferred first-line NRTI backbone. For children who are 3 to 10 years old, TDF/3TC is an alternative first-line NRTI backbone.
- Originator company and product brand name: No originator product exists. The lack of patent barriers in India on both TDF and 3TC meant that generic companies were able to produce this therapeutically interesting FDC.
- First approved by US Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults. 3TC is included as a stand-alone product in the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of originator product: not applicable.

PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

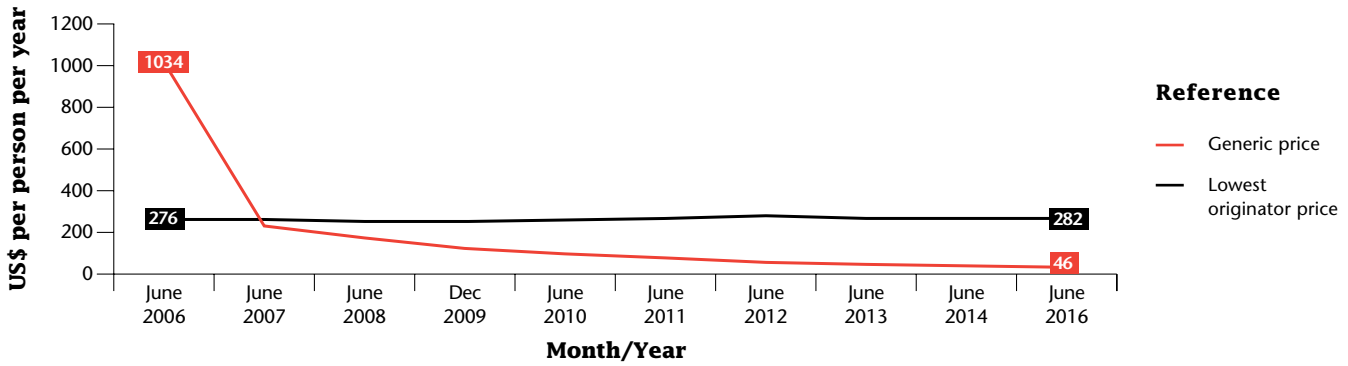
	Daily Dose	Aurobindo	Cipla	Hetero	Macleods	Microlabs	Quality Chemicals	Sun Pharma
TDF/3TC 300/300mg tablet	1	**57 (0.155)**	**58 (0.158)**	**46 (0.125)**	**50 (0.138)**	**47 (0.130)**	**84 (0.230)**	**52 (0.143)**

Evolution of the lowest quoted price for developing countries since 2006:
As of May 2016, there are eight generic sources for TDF/3TC 300/300mg tablets which are quality assured by US FDA or WHO prequalification, seven of which quoted a price this year. The lowest price is shown here.

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

Since 2006, the generic price has decreased by 95%.

TDF/3TC 300/300MG TABLET



SPOTLIGHT ON ACCESS ISSUES

3TC is an equivalent alternative to FTC, as it is structurally related, shares the same efficacy against HIV and HBV, and has the same resistance profile;[1] therefore, this formulation is interchangeable with TDF/FTC. FTC-based FDCs continue to be priced higher than 3TC. There are multiple quality-assured generic formulations of TDF/3TC available; the lowest price is US$46 PPPY, compared to $64 PPPY for TDF/FTC.

PAEDIATRICS

TDF/3TC is an alternative first-line treatment option for children aged 3 to 10 years, but there is no fixed-dose option available for paediatrics, and children requiring it would have to take each drug separately.

The US FDA approved TDF for use in children over two years of age in January 2012. The approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets, but the paediatric formulations are only available from Gilead; there are still no quality-assured generic paediatric versions available.

There are four WHO-prequalified generic sources for 3TC oral solution – the lowest reported price is $23 PPPY. The oral solution formulation of lamivudine may become more important, due to WHO recommendations for earlier neonatal treatment. The preferred treatment for infants 0-2 weeks old is zidovudine (AZT) + 3TC + nevirapine (NVP); for infants aged 2 weeks to 3 months old, the preferred treatment is abacavir (ABC) or AZT + 3TC + lopinavir/ritonavir (LPV/r) syrup. As such, 3TC oral solution was added back to the limited use category of the 2016 IATT paediatric formulary.[2]

PATENTS (ON TDF/3TC)

Patents related to TDF or to 3TC also affect this combination, as neither of the individual components are currently patented in India, this combination is produced by several Indian generics companies.

In October 2012, the Brazilian government announced the introduction of two new FDCs: TDF/3TC (300/300mg) and TDF/3TC/EFV (efavirenz) (300/300/600mg).[3]

Gilead has signed voluntary licences bilaterally, and also through the Medicines Patent Pool (MPP) on TDF and related antiretrovirals. More details of these licences and their impact on access can be found in the product profiles of TDF and 3TC, see below.

Patent barriers related to 3TC are minimal, as the basic patent held by IAF Biochem expired in most countries in 2010. Several WHO prequalified or FDA-approved generics manufacturers are already making this drug.

A new formulation patent has also been filed in many countries.[4,5] This patent was granted in Brazil, China, and in ARIPO and OAPI countries, and will not expire before 2018.[6] In addition, patent applications on specific combinations could create access barriers to 3TC-containing FDCs in countries where combination patents might be granted.[5] This, for instance, would involve FDCs of dolutegravir (DTG)/3TC/ABC; more details are available from the DTG and ABC profiles.

In November 2012, Ecuador issued a compulsory licence on key patents related to ABC and 3TC to manufacture ABC/3TC. The licence was issued to Ecuadorean manufacturer Acroxmax, in a bid to reduce the price by 75%.[7]

In March 2016, GlaxoSmithKline (GSK) made a statement[8] on its future policy of patenting in developing countries, including the waiver of filing patent applications on its new drugs in Least-Developed Countries (LDCs), which already benefit from a waiver from implementing TRIPS obligations on pharmaceutical patents until 2033. It remains unclear whether GSK will withdraw granted patents on the 3TC formulation and combinations in LDCs, including those in ARIPO and OAPI jurisdictions.

PATENTS (ON TDF)

The Academy of Sciences of the former Czechoslovakia applied for the basic patent on TDF in 1986; it has now expired in most countries.[9] Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997, and patents related to the fumarate salt of tenofovir disoproxil in 1998.[10] These are due to expire in 2017 and 2018, respectively. Gilead and BMS have also applied for some combination patents concerning TDF/FTC, TDF/FTC/EFV and TDF/FTC/rilpivirine (RIL), which, where granted, will not expire before 2024 and 2026, respectively.[6]

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Patent oppositions and compulsory licences: expanding spaces for access

The price of TDF has fallen dramatically since 2005, due to generic production that started in India, and thanks to patent oppositions filed by civil society groups.[11] In a major victory for access to medicines, the Indian patent office rejected several patent applications in September 2009 relating to the pro-drug,[12] the fumarate form,[13] the intermediate,[14] the combination of TDF with FTC,[15] and the once-a-day pill TDF/FTC/EFV.[16] In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.[17] After the Brazilian government declared TDF as a medicine of public interest and the Brazilian patent office rejected the patent in September 2008,[5] Gilead launched a legal challenge against the patent office's decision in January 2010, which is still pending. Gilead also requested a divisional patent, which was opposed by civil society groups[18] and then rejected in May 2011[19] - another victory for access to medicines.

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including TDF and its combination with FTC and EFV. This licence will last until the end of the patent period in November 2024.[20]

In July 2013, the Patent Re-Examination Board of China's State Intellectual Property Office declared that one of the earlier granted patents on TDF, CN98807435.4, was invalid. This was a significant decision that occurred after China made changes in its patent law.[21] Generic competition was not automatically triggered after invalidation of this patent, as other blocking patents related to TDF are still valid in China, especially two layers of divisional patents on CN98807435.4 that remain valid. The first layer has two divisional patents (1) 200410046290.X and (2) 200710196265. In addition, the divisional patent (1) has a sub-divisional patent (200510099916), which has also been granted.[22] These divisional patents in China remain unchallenged, to date. In addition, the pro-drug patent of TDF (CN97197460.8) remains valid and unchallenged, while its equivalent patent has been rejected in India.

However, the patent invalidation set an important precedent in China, since it scrutinized pharmaceutical patents that had been wrongly granted. If all relevant patent barriers on TDF were removed, affordable generic once-daily TDF-based FDCs would improve patient outcomes in China, and people with hepatitis B would be able to access life-saving treatment at a more affordable price.

Voluntary licencing and its impact on access

Gilead signed problematic voluntary licensing (VL) agreements in 2006 with key generics manufacturers in India and South Africa, with control over the manufacture and distribution of the active pharmaceutical ingredient (API) and the finished product that excluded a number of countries (including middle-income countries with a substantial burden of HIV).[23] In July 2011, Gilead signed a licence agreement with the MPP concerning a range of products: TDF, FTC and cobicistat (COBI), elvitegravir (EVG), and the 'Quad' (TDF/FTC/COBI/EVG).[24] After receiving criticism from civil society about the limitations contained in its first agreement,[25,26] the MPP licence has been amended several times, with an expansion to include tenofovir alafenamide (TAF) in its July 2014 amendment, and a June 2015 amendment to make manufacturers from China and South Africa eligible to join as sub-licencees. These amendments have changed the situation from its first licence, when only generics producers from India were previously eligible to join.[27]

The amendments have helped to expand the scope, and improved some terms and conditions of the licence, such as inclusion of the hepatitis B indication for TDF, and inclusion of TAF, applying the same terms and conditions for generics production and supply.[28] With these amendments, both Chinese and South African generics manufacturers are eligible to join as sub-licencees, provided that they hold the Good Manufacturing Practice (GMP) qualifications that the licence requires.[29] However, some high burden and generics-producing countries remain excluded from its territory for generic supply, such as Brazil and China; Chinese companies can only join the licence and produce for other countries' markets, not for their own home populations.

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TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE (TDF/FTC)

GENERAL INFORMATION

- **Therapeutic class:** One nucleotide reverse transcriptase inhibitor (NtRTI) and one nucleoside reverse transcriptase inhibitor (NRTI) in a fixed-dose combination (FDC).
- **2016 WHO Guidelines:** TDF/FTC is recommended as part of first-line treatment for adults, pregnant and breastfeeding women, adolescents, and people co-infected with tuberculosis (TB) or hepatitis B virus (HBV). For adolescents above the age of 10, TDF/FTC is the preferred first-line NRTI backbone.
- Originator company and product brand name: Gilead; Truvada.
- First approved by US Food and Drug Administration (FDA): August 2004.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults; not included in the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of originator product: 2015: US$3.459 billion; 2014: $3.340 billion; 2013: $3.136 billion 2012: $3.2 billion; 2011: $2.9 billion; 2010: $2.7 billion; 2009: $2.5 billion; 2008: $2.1 billion; 2007: $1.6 billion; 2006: $1.2 billion; 2005: $568 million; 2004: $68 million.[1]

PRICE INFORMATION

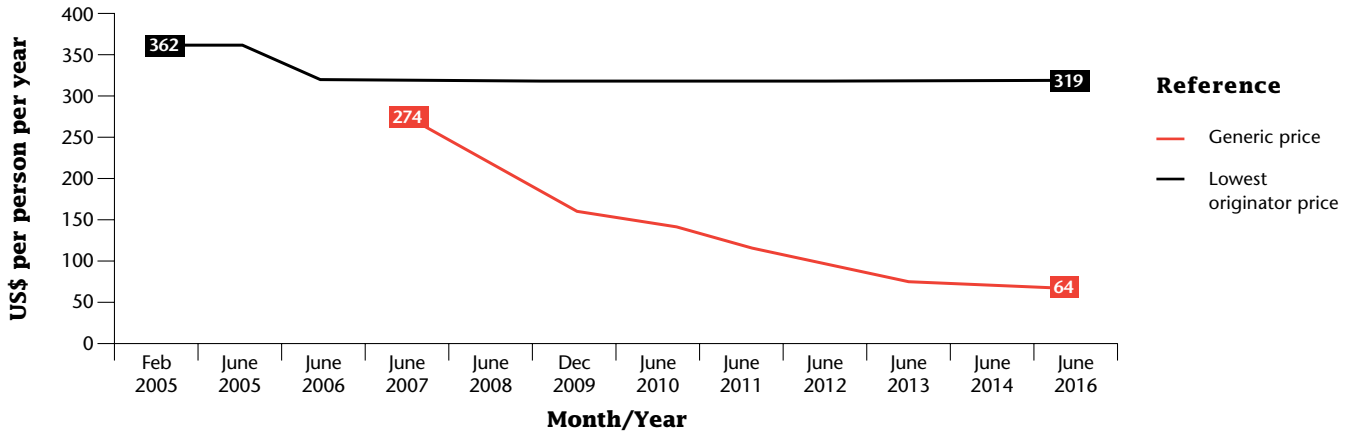
Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Gilead		Aurobindo	Cipla	Hetero	Macleods	Strides
		Low-income countries	Lower middle-income countries					
TDF/FTC 300/200mg tablet	1	**319 (0.875)**	**548 (1.500)**	**72 (0.197)**	**70 (0.192)**	**64 (0.175)**	**77 (0.210)**	**67 (0.183)**

Evolution of the lowest quoted price for developing countries since 2005:
As of May 2016, there are six generic sources of TDF/FTC 300/200mg tablet, which are quality assured by US FDA and/or WHO prequalified, five of which quoted a price this year.

Since 2005 the originator price decreased by almost 12%, and the generic price decreased by almost 77% since 2007.

TDF/FTC 300/200MG TABLET



SPOTLIGHT ON ACCESS ISSUES

FTC is an equivalent alternative to 3TC as it is structurally related, shares the same efficacy against HIV and hepatitis B virus (HBV), and has the same resistance profile;[2] therefore, this formulation is interchangeable with TDF/3TC.

PAEDIATRICS

TDF/FTC is an alternative first-line treatment option for children who are 3 to 10 years of age, and it can be used as an alternative for second- and third-line treatment, depending on previous NRTI exposure. There is no fixed-dose option available for paediatrics, so children would have to take each drug separately.

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets, but the paediatric formulations are only available from Gilead; there are still no quality-assured paediatric generic versions available.

PATENTS (ON TDF/FTC)

Most patents related to TDF or to FTC also affect this combination. Gilead applied for patents specifically related to this combination in 2004; they are due to expire in 2024.[3]

The patent on the combination of TDF/FTC has been granted in some developing countries, including China, Russia, South Africa and in ARIPO countries.[3,4] The same patent has been rejected in India*[3,5] and withdrawn in Thailand.[6] It is also under pre-grant opposition proceedings filed by civil society organisations in Brazil in 2010 and 2013,[7] and in Argentina in 2015.[7]

FTC is produced by Indian generics companies under a voluntary licence (VL) from Gilead. However, Cipla – which does not have a VL – is able to produce TDF/FTC because neither of the individual components is patented in India. A divisional patent application related to this combination has also been rejected in India.[8]

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including TDF/FTC. This licence will last until the end of the patent period in November 2024.[9]

PATENTS (ON FTC)

The basic patents on FTC and lamivudine (3TC) expired between 2010 and 2011 in most countries.[3] Gilead filed combination patents containing FTC in several countries that expire in 2024 and 2026,[3] which might hinder access to FDCs containing FTC and 3TC.

Gilead has signed bilateral VLs with generics producers, and also signed VLs with the Medicines Patent Pool (MPP) on production and supply of several ARVs, including FTC. More details on the evolution of, and issues with, the licences can be found under patents on TDF **(see below)**.

PATENTS (ON TDF)

The Academy of Sciences of the former Czechoslovakia applied for the basic patent on TDF in 1986; it has now expired in most countries.[10] Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997, and patents related to the fumarate salt of tenofovir disoproxil in 1998.[11] These are due to expire in 2017 and 2018, respectively. Gilead and BMS have also applied for some combination patents concerning TDF/FTC, TDF/FTC/efavirenz (EFV) and TDF/FTC/rilpivirine (RIL), which, where granted, will not expire before 2024 and 2026, respectively.[3]

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*Its divisional application no. 6665/DELNP/2008, was withdrawn.

Continued overleaf

invalidation of this patent, as other blocking patents related to TDF are still valid in China, especially two layers of divisional patents on CN98807435.4 that remain valid. The first layer has two divisional patents (1) 200410046290.X and (2) 200710196265. In addition, the divisional patent (1) has a sub-divisional patent (200510099916), which has also been granted.[21] These divisional patents in China remain unchallenged to date. In addition, the pro-drug patent of TDF (CN97197460.8) remains valid and unchallenged while its equivalent patent has been rejected in India.

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TENOFOVIR DISOPROXIL FUMARATE/ EMTRICITABINE/EFAVIRENZ (TDF/FTC/EFV600)

GENERAL INFORMATION

- **Therapeutic class:** One nucleotide reverse transcriptase inhibitor (NtRTI), one nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in a fixed-dose combination (FDC).
- **2016 WHO Guidelines:** TDF/FTC/EFV is the recommended first-line treatment for adults, pregnant and breastfeeding women, adolescents and people co-infected with tuberculosis (TB) and/or hepatitis B virus (HBV). A lower dose of EFV (400mg vs. 600mg) is recommended as part of an alternative first-line regimen for adults and adolescents who are at least 12 years old **(see Spotlight on Access).**
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb (BMS)/Merck; Atripla.
- First approved by US Food and Drug Administration (FDA): July 2006.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults. EFV is also included as a stand-alone product in the 5th edition for children. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of FDCs and the development of appropriate new FDCs.
- World sales of the originator: 2015: US$3.134 billion; 2014: $3.470 billion; 2013: $3.648 billion; 2012: $3.6 billion; 2011: $3.2 billion; 2010: $2.9 billion; 2009: $2.4 billion; 2008: $1.6 billion; 2007: $903 million; 2006: $164 million.[1]

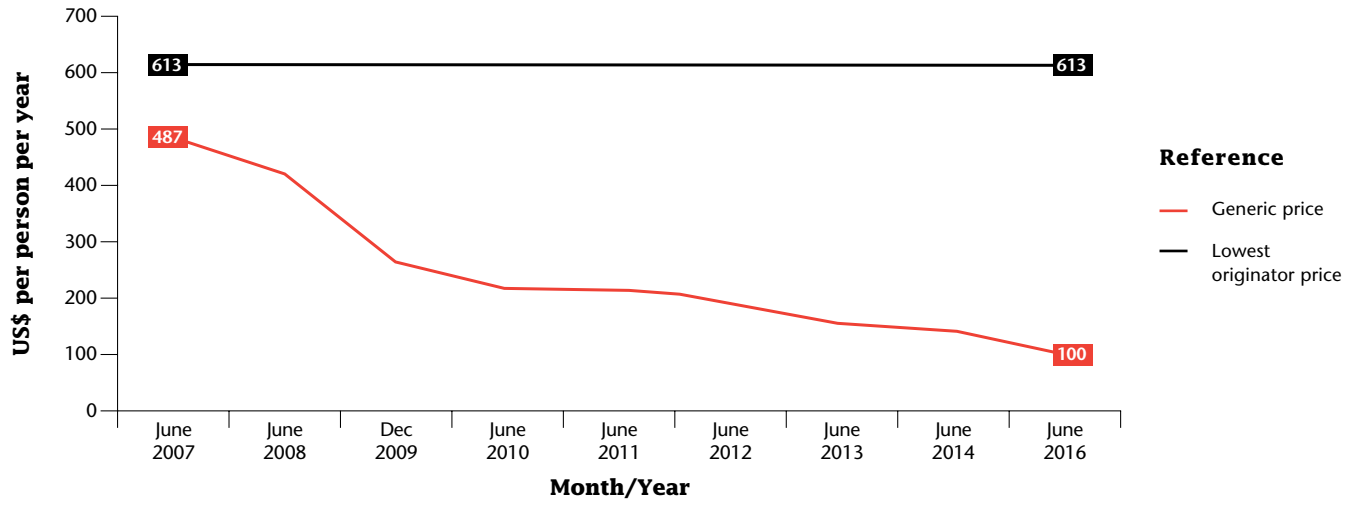
PRICE INFORMATION

Developing country prices in US$ per person per year (PPPY), as quoted by companies.
The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold**.

	Daily Dose	Merck		Aspen	Aurobindo	Cipla	Hetero	Macleods	Strides	Sun Pharma
		Category 1 countries	Category 2 countries							
TDF/FTC/EFV 300/200/600mg tablet	1	**613 (1.680)**	**1033 (2.830)**	251 (0.689)	**112 (0.307)**	**122 (0.333)**	**110 (0.300)**	**120 (0.328)**	**103 (0.283)**	**100 (0.273)**

Evolution of the lowest quoted price for developing countries since 2005:
There are currently six quality-approved generic sources of TDF/FTC/EFV_{600}; the lowest price for this WHO-prequalified generic product is US$100 PPPY, which – for the first time – is less than the lowest reported price for TDF/3TC/EFV (at $106 PPPY).

TDF/FTC/EFV 300/200/600MG TABLET



At the time this went to press, several generics companies were developing TDF/XTC/EFV_{400}; none were quality-assured yet. One price was provided for TDF/3TC/EFV_{400} at $97 PPPY. Mylan Laboratories has announced that it will file for US FDA tentative approval for an alternate first-line FDC containing tenofovir disoproxyl fumarate, lamivudine and a reduced dose of efavirenz (400mg vs. 600mg) in Q1 2016, and make it available for $99 PPPY, subject to regulatory approval.[2]

SPOTLIGHT ON ACCESS ISSUES

The originator version of TDF/FTC/EFV, marketed as Atripla, was the first triple-class antiretroviral FDC approved by the US FDA (in July 2006), and was the first collaboration between two US pharmaceutical corporations combining patented HIV medicines into one product (Gilead's TDF and FTC with Bristol-Myers Squibb's EFV).[3] Atripla is jointly marketed in North America and Europe by Gilead and BMS; marketing and distribution in much of the developing world is handled by Merck.[4]

TDF/FTC/EFV_{600} is an easy to use, one-pill-a-day FDC that continues to be recommended as the preferred first-line treatment option for adolescents and adults, pregnant and breastfeeding women, and during treatment for TB co-infection.

As an alternative option for first-line treatment, the same combination – with a lower dose of EFV (400mg) (TDF/FTC/EFV_{400}) – can be used in adults and adolescents from 12 years of age. It has been shown to be as effective as TDF/FTC/EFV_{600}, with a better adverse event profile.[5] WHO requires further data before EFV_{400} can be recommended during pregnancy, breastfeeding, rifampicin-based TB treatment, and in children under 12 years of age.[6]

FTC is an equivalent alternative to 3TC since it is structurally related, shares the same efficacy against HIV and HBV, and has the same resistance profile;[7] therefore, these formulations are interchangeable with TDF/3TC/EFV.

PAEDIATRICS

TDF/FTC/EFV is an alternative first-line treatment option for children ages 3 to 10, but there is no fixed-dose option for paediatrics; children have to take each drug separately. EFV 200mg tablets continue to be on the IATT optimal formulary list.[8]

The US FDA approved TDF for use in children over two years of age in January 2012. Approved formulations include a 40mg/gr oral powder and 150mg, 200mg, 250mg and 300mg tablets, but the paediatric formulations are only available from Gilead; there are still no quality-assured generics available.

PATENTS (ON TDF/FTC/EFV)

Most patents related to TDF, FTC, TDF/FTC or EFV also affect this combination. Gilead and BMS jointly applied for patents specifically related to this combination in 2006,[9] which will last until 2026.

None of the individual components are currently patented in India, so this combination is produced by several Indian generics companies. Gilead filed a patent application related to the combination of TDF/FTC/EFV,[10] which was challenged by generics producers through pre-grant oppositions[11] and rejected by the Indian patent office.[12]

In December 2013, people living with HIV in Argentina filed oppositions against patent applications covering TDF/FTC/EFV.[11,13] Since Argentina adopted new guidelines for the examination of pharmaceutical patents in May 2012, several low-quality patent applications have been rejected due to a lack of novelty and inventive step. In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including on TDF/FTC/EFV. This licence will last until the patent expires in November 2024.[14]

Gilead has signed a number of voluntary licence deals with Indian manufacturers on TDF and TDF-based combinations, and entered into the licence agreement with the Medicines Patent Pool (MPP) in 2011, on TDF and other related ARVs.

The basic patent on EFV was filed by Merck in 1993 and expired in most countries in August 2013.[15] Gilead and BMS jointly filed patent applications on the combination of EFV with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), which will not expire before 2026 in countries where the patent applications have been granted.[16]

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Compulsory licences and anti-competition complaints

In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government started purchasing EFV at $106 per person, per year (PPPY) – considerably lower than the previous price of $511 PPPY at that time.[17]

In May 2007, Brazil – after numerous unsuccessful negotiations with Merck – issued a compulsory licence to import more affordable generic versions from India.[18,19] At the time, the price of EFV in Brazil was $580 PPPY and had not changed since 2003. After the compulsory licence, Brazil began to import a WHO-prequalified generic version for $190 PPPY. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched a locally-produced generic version for use in the Brazilian health system.[20]

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including EFV. This licence lasted until the patent expired in August 2013.[14]

In South Africa, Merck's refusal to allow sufficient generic competition contributed significantly to the high price of the drug. This led the AIDS Law Project - acting on behalf of the Treatment Action Campaign - to file a complaint before the Competition Commission in November 2007. As a result, Merck agreed to licence its product to other producers, opening the opportunity for generic competition in South Africa, where six suppliers now market EFV or EFV-containing combination products.[21]

Generic supplies

In view of the main patent expiry in August 2013, several generics companies attempted to launch their versions of EFV. Multiple patent infringement cases were filed in the United States and elsewhere to block early generic competition. Some of these cases were decided in Merck's favour, which has delayed the launch of generic versions of EFV in the United States.[22]

To foster future competition and ensure supply security, the Kirby Institute and the Clinton Health Access Initiative (CHAI) have agreed to make the study data available to companies seeking to develop other generic versions, including a FDC containing TDF/3TC/EFV_{400} (named TLE400).[23]

PATENTS (ON FTC)

The basic patents on FTC and lamivudine (3TC) expired between 2010 and 2011 in most countries.[16] Gilead filed combination patents containing FTC in several countries expiring in 2024 and 2026,[16] which might hinder access to FDCs containing FTC and 3TC.

Gilead has signed bilateral voluntary licences with generics producers, and signed voluntary licences with the Medicines Patent Pool on production and supply of several ARVs, including FTC. For more details of the evolution of, and issues with, the licences, see PATENTS (ON TDF), below.

PATENTS (ON TDF)

The Academy of Sciences of the former Czechoslovakia applied for the basic patent on TDF in 1986; it has now expired in most countries.[24] Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997, and patents related to the fumarate salt of tenofovir disoproxil in 1998.[25] These are due to expire in 2017 and 2018, respectively. Gilead and BMS have also applied for some combination patents concerning TDF/FTC, TDF/FTC/EFV and TDF/FTC/rilpivirine (RIL), which, where granted, will not expire before 2024 and 2026 respectively.[16]

Patent oppositions and compulsory licences: expanding spaces for access

The price of TDF has fallen dramatically since 2005, due to generic production that started in India, and thanks to patent oppositions filed by civil society groups.[26] In a major victory for access to medicines, the Indian patent office rejected several patent applications in September 2009 relating to the pro-drug,[27] the fumarate form,[28] the intermediate,[29] the combination of TDF with FTC,[30] and the once-a-day pill TDF/FTC/EFV.[31]

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.[32] After the Brazilian government declared TDF as a medicine of public interest and the Brazilian patent office rejected the patent in September 2008,[16] Gilead launched a legal challenge against the patent office's decision in January 2010, which is still pending. Gilead also requested a divisional patent, which was opposed by civil society groups,[33] and then rejected, in another victory for access to medicines, in May 2011.[34]

In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including TDF and its combination with FTC and EFV. This licence will last until the end of the patent period in November 2024.[14]

In July 2013 the Patent Re-Examination Board of China's State Intellectual Property Office declared that one of the earlier granted patents on TDF, CN98807435.4, was invalid. This was a significant decision that occurred after China made changes in its patent law.[35] Generic competition was not automatically triggered after the invalidation of this patent, as other blocking patents related to TDF are still valid in China, especially two layers of divisional patents

on CN98807435.4. The first layer has two divisional patents (1) 200410046290.X and (2) 200710196265. In addition, the divisional patent (1) has a sub-divisional patent (200510099916), which has also been granted.[36]

These divisional patents in China remain unchallenged to date. In addition, the pro-drug patent of TDF (CN97197460.8) remains valid and unchallenged while its equivalent patent has been opposed in India.

However, the patent invalidation was an important precedent in China, since it scrutinized pharmaceutical patents that had been wrongly granted. If all relevant patent barriers on TDF were removed, affordable generic once daily TDF-based FDCs would immediately improve patient outcomes in China, and people with hepatitis B would be able to access life-saving treatment at a more affordable price.

Voluntary licencing and its impact on access

Gilead signed problematic voluntary licensing (VL) agreements in 2006 with key generics manufacturers in India and South Africa, with control over the manufacture and distribution of the active pharmaceutical ingredient (API) and the finished product that excluded a number of countries (including middle-income countries with a substantial burden of HIV).[37] In July 2011, Gilead signed a licence agreement with the MPP concerning a range of products: TDF, FTC and cobicistat (COBI); elvitegravir (EVG), and the 'Quad' (TDF/FTC/COBI/EVG).[38] After receiving criticism from civil society about the limitations contained in its first agreement,[39,40] the MPP licence has been amended several times, with an expansion to include tenofovir alafenamide (TAF) in its July 2014 amendment, and a June 2015 amendment to make manufacturers from China and South Africa eligible to join as sub-licencees; these amendments have changed the situation from its first licence when only generics producers from India were previously eligible to join.[41]

The amendments have helped to expand the scope and improved some terms and conditions of the licence, such as inclusion of the hepatitis B indication for TDF, and inclusion of TAF, applying the same terms and conditions for generic production and supply.[41] With these amendments, both Chinese and South African generics manufacturers are eligible to join as sub-licencees, provided that they hold the Good Manufacturing Practice (GMP) qualifications that the licence requires.[42] However, some high burden and generics-producing countries remain excluded from its territory for generic supply, such as Brazil and China; Chinese companies can only join the licence and produce for other countries' markets, not for their own home populations.

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ANNEX 1: SUMMARY TABLE OF ALL PRICES

Developing country prices in US$ per person per year, as quoted by companies.
This table contains comprehensive information about ARV pricing in developing countries. It includes adult and paediatric formulations and doses, suppliers and WHO pre-qualification status/US FDA/stringent regulatory authority approval. The prices for developing countries are in US $, per person, per year, based on WHO dosing recommendations, as quoted by companies. Currency conversions were made when the pricing information was received, using the currency converter from www.oanda.com.

Each originator company applies its own eligibility criteria for discounting ARVs. Countries that are eligible for a discount from one company may not be eligible for discounts from other companies. Usually, companies create two groups of discount-eligible countries, often called 'Category 1' (countries that are eligible for the deepest discounts) and 'Category 2' (countries that are offered a lesser discount).

Paediatric formulations are highlighted in pink. Prices for paediatric products are estimated, based on WHO-recommended dosing, for the 10kg to 10.9kg weight band. When it was not possible to calculate dosing for the 10kg weight band, the unit price was used.

The ARVs that are included in the WHO list of Prequalified Medicinal Products or that have tentative or full US FDA approval (as of May 2016) are in **bold**.

ARVs in alphabetical order	**Daily dose**	**Originator company**		**Generics companies**									
Abacavir (ABC)		ViiV		Aspen	Aurobindo	Cipla	Hetero						
20mg/ml oral solution	12 ml	**289 (0.066)**		249 (0.057)	**228 (0.052)**		**123 (0.028)**						
60mg tablet	4					**97 (0.067)**							
Atazanavir (ATV)		BMS		Aspen	Cipla	Emcure							
		Category 1 countries	Category 2 countries										
100mg capsule	xx					**(0.267)**							
150mg capsule	2	**412 (0.564)**	**412 (0.564)**	380 (0.520)		**207 (0.283)**							
200mg capsule	xx	**(0.677)**	**(0.677)**	(0.670)		**(0.433)**							
300mg capsule	1				170 (0.467)	**219 (0.600)**							
Atazanavir/ ritonavir (ATV/r)				Cipla	Emcure	Hetero							
300/100mg tablet	1			213 (0.583)	**213 (0.583)**	219 (0.600)							
Darunavir (DRV)		Janssen		Aspen	Hetero								
75mg tablet	xx	**(0.114)**											
150mg tablet	xx	**(0.227)**											
400mg tablet	2	**438 (0.600)**			**973 (1.333)**								
600mg tablet	2	**663 (0.908)**		**658 (0.901)**	**1,217 (1.667)**								
Efavirenz (EFV)		Merck		Aspen	Aurobindo	Cipla	Emcure	Hetero	Macleods	Microlabs	Quality Chemicals	Strides	Sun Pharma
		Category 1 countries	Category 2 countries										
30mg/ml suspension	xx	**(0.094)**	**Case-by-case**										
50mg capsule	xx				**(0.058)**					**(0.057)**			
50mg tablet	xx	**(0.114)**	**Case-by-case**										
200mg capsule	3				**81 (0.074)**					**57 (0.052)**			
200mg tablet	3	**394 (0.360)**	**Case-by-case**									**113 (0.103)**	
600mg tablet	1	**237 (0.650)**	**Case-by-case**	84 (0.231)	**37 (0.100)**	**20 (0.055)**	**47 (0.129)**	**45 (0.123)**	**38 (0.105)**	**35 (0.095)**	**70 (0.192)**	**38 (0.105)**	**38 (0.103)**

ARVs in alphabetical order	Daily dose	Originator companies		Generics companies									
Etravirine (ETV)		Janssen		Aspen									
25mg tablet	xx	**(0.075)**											
100mg tablet	4	**438 (0.300)**		**438 (0.300)**									
Lamivudine (3TC)		ViiV		Aspen	Aurobindo	Cipla	Hetero	Macleods	Microlabs	Strides	Sun Pharma		
10mg/ml oral suspension	10ml	**216 (0.059)**			**23 (0.006)**	**46 (0.013)**	**32 (0.009)**	**26 (0.007)**					
150mg tablet	2	**75 (0.102)**		**55 (0.075)**	**27 (0.037)**	**28 (0.038)**	**29 (0.040)**	**23 (0.031)**	**23 (0.031)**	**27 (0.037)**	**26 (0.035)**		
300mg tablet	1	**75 (0.204)**				**33 (0.092)**	**32 (0.087)**	**23 (0.063)**	**18 (0.049)**	**67 (0.183)**			
Lopinavir/ ritonavir (LPV/r)		Abbvie		Aurobindo	Cipla	Hetero	Macleods						
		Category 1 countries	Category 2 countries										
80/20mg/ml oral solution	4ml	**150 (0.103)**	**296 (0.203)**										
40mg/10mg capsule heat-stable pellets	8				**467 (0.160)**								
100/25mg heat-stable tablet	3	**108 (0.099)**	**278 (0.254)**	**151 (0.138)**	155 (0.142)		**143 (0.131)**						
200/50mg heat-stable tablet	4	**231 (0.158)**	**740 (0.507)**	**243 (0.167)**	**268 (0.183)**	**280 (0.192)**	**293 (0.201)**						
Nevirapine (NVP)				Aspen	Aurobindo	Cipla	Emcure	Hetero	Macleods	Microlabs	Quality Chemicals	Strides	Sun Pharma
10mg/ml suspension	20ml				**61 (0.008)**	**91 (0.013)**							
50mg tablet for oral suspension	4				**73 (0.050)**	**30 (0.021)**							
200mg capsule	2												
200mg tablet	2			**63 (0.087)**	**28 (0.038)**	**28 (0.038)**	**28 (0.038)**	**29 (0.040)**	**27 (0.037)**	**24 (0.033)**	**37 (0.051)**	**27 (0.037)**	**26 (0.035)**
Raltegravir (RAL)		Merck		**Hetero**									
		Category 1 countries	Category 2 countries										
25mg chewable tablet	xx	**(0.300)**	**Case-by-case**										
100mg chewable tablet	xx	**(0.600)**	**Case-by-case**										
400mg tablet	2	**675 (0.925)**	**Case-by-case**	**973 (1.333)**									
Ritonavir (RTV)		Abbvie											
		Category 1 countries	Category 2 countries										
80mg/ml oral solution	xx	**(0.091)**	**Case-by-case**										
100mg heat-stable tablet	2	**83 (0.114)**	**Case-by-case**										
Tenofovir (TDF)		Gilead		Aurobindo	Cipla	Hetero	Macleods	Quality Chemicals	Strides	Sun Pharma			
		Category 1 countries	Category 2 countries										
300mg tablet	1	**207 (0.567)**	**365 (1.000)**	**57 (0.155)**	**46 (0.127)**	**39 (0.107)**	**40 (0.110)**	*67* (0.183)	**45 (0.123)**	**43 (0.117)**			

ARVs in alphabetical order	Daily dose	Originator companies		Generics companies								
Zidovudine (AZT)		ViiV		Aurobindo	Cipla	Hetero	Macleods	Microlabs	Sun Pharma			
10mg/ml oral solution	24ml	**450 (0.051)**		**73 (0.008)**	**110 (0.013)**		**91 (0.010)**					
60mg tablet	4							**40 (0.027)**				
100mg capsule	xx	**(0.093)**		**(0.055)**								
250mg capsule	xx	**(0.187)**										
300mg tablet	2			**69 (0.094)**	**67 (0.092)**	**75 (0.103)**		**63 (0.086)**	**50 (0.068)**			
ABC/3TC		ViiV		Aurobindo	Cipla	Hetero						
60/30mg tablet	4			**110 (0.075)**	**110 (0.075)**							
600/300mg tablet	1	**225 (0.617)**		**220 (0.602)**	**164 (0.450)**	**161 (0.442)**						
TDF/FTC		Gilead		Aurobindo	Cipla	Hetero	Macleods	Strides				
		Category 1 countries	Category 2 countries									
300/200mg tablet	1	**319 (0.875)**	**548 (1.500)**	**72 (0.197)**	**70 (0.192)**	**64 (0.175)**	**77 (0.210)**	**67 (0.183)**				
TDF/FTC/EFV		Merck		Aspen	Aurobindo	Cipla	Hetero	Macleods	Strides	Sun Pharma		
		Category 1 countries	Category 2 countries									
300/200/600mg tablet	1	**613 (1.680)**	**1033 (2.830)**	251 (0.689)	**112 (0.307)**	**122 (0.333)**	**110 (0.300)**	**120 (0.328)**	**103 (0.283)**	**100 (0.273)**		
TDF/3TC				Aurobindo	Cipla	Hetero	Macleods	Microlabs	Quality Chemicals	Sun Pharma		
300/300mg tablet	1			**57 (0.155)**	**58 (0.158)**	**46 (0.125)**	**50 (0.138)**	**47 (0.130)**	**84 (0.230)**	**52 (0.143)**		
TDF/3TC/EFV				Aurobindo	Cipla	Hetero	Macleods	Quality Chemicals				
300/300/400mg tablet	1					97 (0.265)						
300/300/600mg tablet	1			**110 (0.300)**	**110 (0.300)**	**106 (0.292)**	**106 (0.292)**	161 (0.440)				
TDF/3TC+NVP (co-pack)				Hetero								
300/300 + 200mg co-pack	1 kit (3 tabs)			**124 (0.340)**								
AZT/3TC		ViiV		Aurobindo	Cipla	Emcure	Hetero	Macleods	Microlabs	Quality Chemicals	Strides	Sun Pharma
60/30mg tablet	4			**54 (0.037)**	**46 (0.032)**				**46 (0.032)**			
300/150mg tablet	2	**161 (0.221)**		**82 (0.113)**	**82 (0.113)**	**127 (0.173)**	**84 (0.115)**	**84 (0.113)**	**73 (0.100)**	**116 (0.159)**	**76 (0.104)**	**74 (0.102)**
AZT/3TC/ABC				Sun Pharma								
60/30/50mg tablet	3			420 (0.383)								
AZT/3TC/NVP				Aurobindo	Cipla	Hetero	Macleods	Quality Chemicals	Strides	Sun Pharma		
60/30/60mg tablet	4				**88 (0.060)**				**80 (0.055)**			
300/150/200mg tablet	2			**97 (0.133)**	**96 (0.132)**	**95 (0.130)**	**102 (0.139)**	**126 (0.173)**	**94 (0.129)**	**96 (0.131)**		
AZT/3TC + EFV (co-pack)				Aurobindo	Strides							
300/150 + 600mg tablets (co-packs)	1 kit (3 tabs)			**164 (0.450)**	**170 (0.467)**							

ANNEX 2: CONDITIONS OF OFFER

Definitions of eligibility vary from company to company. Each originator company establishes different restrictions to their offer of reduced prices, and classifies countries according to different categories. This lack of uniformity leads to significant differences in a country's eligibility for different products. Some companies resort to the least-developed country (LDC) classification developed by the United Nations (which are updated every few years); others to World Bank classifications concerning country income (which are updated annually); others still to geographical criteria (which may be subjective). Lists provided by companies may differ from the classifications developed by the United Nations or the World Bank. The conditions detailed in the table below were those quoted by companies, unless specified.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
AbbVie	**Category 1 Countries:** All African countries and all United Nations-defined Least-Developed Countries (LDCs) outside of Africa; Afghanistan, Algeria, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo Brazzaville, Congo DR, Côte d'Ivoire, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Laos, Lesotho, Liberia, Libya, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, São Tomé and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, Sudan, Swaziland, Tanzania, Timor-Leste, Togo, Tunisia, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe. **Category 2 Countries:** Albania, Armenia, Azerbaijan, Belarus, Bolivia, Bosnia and Herzegovina, China, Colombia, Dominican Republic, Ecuador, El Salvador, Fiji, Georgia, Guatemala, Guyana, Honduras, India, Indonesia, Jamaica, Jordan, Kazakhstan, Kyrgyzstan, Macedonia, Marshall Islands, Micronesia, Moldova, Mongolia, Montenegro, Nicaragua, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Serbia, Sri Lanka, Suriname, Syria, Tajikistan, Thailand, Tonga, Turkmenistan, Ukraine, Uzbekistan, Vietnam. Preferential pricing does not apply to ritonavir in all Category 2 countries; prices are negotiated on a **case-by-case basis**. Certain ritonavir formulations and package sizes may not be registered or available in some countries. Most notably, this includes ritonavir oral solution. Where products are not registered, vendor will work with buyer to provide documentation for a waiver.	Governments and programs that are fully funded by governments, UN system organisations, NGOs and other not-for-profit institutional providers in low- and lower-middle income countries.		FCA.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Aspen	**Darunavir 600mg:** Burkina Faso, Cameroon, Côte D'Ivoire, Democratic Republic of the Congo, Gabon, Kenya, Lesotho, Mali, Namibia, Nigeria, Tanzania, Uganda, Zambia, Zimbabwe. **Etravirine 100mg:** Botswana, Burkina Faso, Cameroon, Côte D'Ivoire, Democratic Republic of the Congo, Gabon, Ghana, Kenya, Mali, Namibia, Nigeria, Zambia, Zimbabwe.	No restrictions.	All listed prices exclude freight. The freight is done on a shipment to shipment basis. Where the products (excluding darunavir and etravirine listed above) are not registered (within sub-saharan Africa), an import waiver will be required.	Ex-works.
Aurobindo	**All countries except where patent restrictions and regulatory requirements can be a compelling factor.**	No restrictions.	Minimum quantity and freight and insurance are additional as per incoterms, mode of shipment and destination.	Ex-works.
Bristol-Myers Squibb (BMS)	**Category 1 Countries:** Sub-Saharan African countries (with the exception of Southern African countries) plus countries classified as low-income by the World Bank (except Korea, Kyrgyzstan, Moldova and Uzbekistan): Afghanistan, Angola, Bangladesh, Benin, Bhutan, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, Kenya, Laos, Liberia, Madagascar, Mali, Mauritania, Mauritius, Mongolia, Myanmar, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Papua New Guinea, Rwanda, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Sudan, Tanzania, Timor-Leste, Togo, Tuvalu, Uganda, Viet Nam, Yemen. **Category 2 Countries:** Southern African countries: Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia, Zimbabwe. For other developing countries, prices are negotiated on a **case-by-case basis** with local BMS representatives.	No restrictions.	Category 1 countries are invoiced in US$. Category 2 countries are invoiced in South African rand, so as to not have customers impacted by the currency exchange fluctuations, i.e. REYATAZ 150MG CAPS bottle of 60 is ZAR 229.04; REYATAZ 200MG CAPS bottle of 60 is ZAR 274.85. On 12 December 2013, the Medicines Patent Pool (MPP) and BMS signed a licensing agreement to increase access to a key HIV medicine, atazanavir, in 110 countries around the world. This is the MPP's first agreement covering a WHO-preferred second-line therapy. Under the terms of the agreement, a technology transfer package will be provided to sublicensees to facilitate the manufacture of atazanavir. While royalties are not applicable in the vast majority of the countries and are waived for all paediatric products, any royalties that are collected under this licence agreement will be reinvested in local HIV/AIDS groups in those countries.	FCA.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Cipla	Generic accessible countries without any patent restrictions	Governments and programmes that are fully funded by governments, UN system organisations, non-governmental organisations and other not-for profit- institutional providers in low- and lower-middle income countries.		Ex-works.
Emcure	Access countries only. Atazanavir-based formulations will be offered to the 110 countries licensed under the Medicines Patent Pool (MPP) / BMS agreement.	No restrictions.		Ex-works.
Gilead	Based on gross national income (GNI) and HIV prevalence (110 low- income and 12 lower-middle income) **Category 1 Countries:** Gilead includes 110 eligible countries, including all African states and additional countries, based on their economic status (measured by GNI and HIV prevalence). The following list was provided by Gilead: Afghanistan, Algeria, Angola, Anguilla, Antigua and Barbuda, Aruba, Bahamas, Bangladesh, Barbados, Belize, Benin, Bhutan, Bolivia, Botswana, British Virgin Islands, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Cayman Islands, Central African Republic, Chad, Comoros, Congo Republic, Cook Islands, Democratic Republic of Congo, Côte d'Ivoire, Cuba, Curacao, Djibouti, Dominica, Dominican Republic, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Jamaica, Kenya, Kiribati, Kyrgyzstan, Laos (Lao PDR), Lesotho, Liberia, Libya, Madagascar, Malawi, Maldives, Mali, Marshall Islands, Mauritania, Mauritius, Micronesia, Mongolia, Montserrat, Morocco, Mozambique, Myanmar, Namibia, Nauru, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Palau, Papua New Guinea, Rwanda, St Kitts and Nevis, St Lucia, St Vincent and the Grenadines, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone; Solomon Islands, Somalia, South Africa, South Sudan, St. Maarten, Sudan, Suriname, Swaziland, Tajikistan, Tanzania, Timor-Leste, Togo, Trinidad and Tobago, Tunisia, Turks and Caicos, Tuvalu, Uganda, Uzbekistan, Vanuatu, Vietnam, Zambia, Zimbabwe. **Category 2 Countries:** Gilead includes 12 eligible countries in Category 2. The following list was provided by Gilead: Ecuador, El Salvador, Fiji, North Korea, Panama, Paraguay, Peru, Philippines, Sri Lanka, Thailand, Tonga, Turkmenistan.	No restrictions.		FCA Dublin.
Hetero	No restrictions.	No restrictions.		FOB.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
Janssen (J&J)	**Category 1 Countries:** special effort access price for all countries of Sub-Saharan Africa and least developed countries outside of Africa. *The following list was provided by Janssen.* **Category 1:** Afghanistan, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central Africa Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Laos, Lesotho, Liberia, Maldives, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal,Niger, Nigeria, Rwanda, Samoa, São Tomé and Príncipe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Timor-Leste, Togo, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe. For other low- and middle-income countries, differentiated prices are applicable on a **country-by-country basis**.	No restrictions.	The prices are ex-factory based, either supplied via Janssen out of Belgium, or Aspen Pharmacare out of South Africa, depending on the regulatory status of the relevant formulation in the destination country. With respect to paediatric formulations, countries that have qualified under the New Horizon Collaborative receive medication for treatment of children free of charge. In addition, Janssen extended its policy of non-enforcement of darunavir patents for paediatric formulations in to up to 128 countries in support of the PHTI project.	FOB Johannesburg for sub-Saharan African countries with marketing authorization for the relevant formulation in country of destination, and FOB Belgium for all other sub-Saharan African countries, plus least developed countries outside of Africa.
Macleods	No restrictions.	No restrictions.		Ex-works.
Merck	Category 1 countries are eligible for Merck's access price (including all sub-Saharan Africa, all LDCs, all low-income countries and the following list) : Afghanistan , Angola, Bangladesh, Benin, Bhutan, Botswana; Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Democratic Republic, Congo Republic, Cote d'Ivoire, Djibouti, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Haiti, India, Kenya, Kiribati, Korea Democratic Republic, Lao PDR, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Rwanda, Samoa, São Tomé and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tajikistan, Tanzania, Timor-Leste, Togo, Tuvalu, Uganda, Vanuatu, Yemen, Zambia, Zimbabwe. In other MICs, price is established on **case-by-case basis**.	Governments and programmes that are fully funded by governments and/or by multi- and bi-lateral donors (such as The Global Fund, PEPFAR, UNITAID); UN system organisations, non-governmental organisations and other non-commercial providers of HIV treatment	Merck/MSD has signed three voluntary license agreements for the RAL 400mg tablet, and in 2015, signed an agreement with the MPP which covers the paediatric formulations.	CIP.
Micro Labs	All countries, except India	All organisations.		FCA.
Quality Chemicals	No restrictions.	No restrictions.		Ex-Works.
Strides	No restrictions.	No restrictions.		FCA Bangalore, India.
Sun Pharmaceutical	These prices are valid for the Generic Access Market countries, mostly low-income countries.	These prices are valid for NGOs.		FCA.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
ViiV	ViiV has licensed its patents directly to 17 generic companies and also to MPP for a wide range of countries. ViiV licenses adult formulations of its ARVs to all LDCs, LICs and all sub-Saharan countries, 67 in total; and paediatric formulations to 121 countries. All ViiVs established ARV portfolio for this territory is preferentially priced at a fixed at-cost price (not volume dependent or yearly evaluation). The 67 countries for adult formulations are as follows (this list was provided by ViiV): Afghanistan, Angola, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Djibouti, DR Congo, East Timor, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Ghana, Gambia, Guinea, Guinea-Bissau, Haiti, Kenya, Kiribati, Lao People's DR, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Democratic People's Republic of North Korea, Republic Kyrgyz, Rwanda, Samoa, São Tomé and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Tajikistan, Togo, Tuvalu, Uganda, Vanatu, Yemen, Zambia, Zimbabwe. The 121 countries for Paediatric Formulations are as follows (this list was provided by ViiV): Afghanistan, Algeria, Angola, Argentina, Armenia, Azerbaijan, Bangladesh, Belize, Benin, Bhutan, Bolivia, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Chile, Colombia, Comoros, Congo Republic, Costa Rica, Cote d'Ivoire, Cuba, Djibouti, Democratic Republic of Congo, Dominican Republic, East Timor, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gabon, Gambia, Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Haiti, Honduras, India, Indonesia, Iran, Iraq, Jamaica, Kenya, Kiribati, Kosovo, Lao People's DR, Lebanon, Lesotho, Liberia, Libya, Madagascar, Malawi, Malaysia, Maldives, Mali, Marshall Isalnds, Mauritania, Mauritius, Micronesia, Moldova Republic of, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nauru, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Palau, Papua New Guinea, Panama, Paraguay, Peru, Philippines, Republic Kyrgyz, Democratic People's Republic of Korea, Rwanda, Samoa, São Tomé and Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia, South Africa, South Sudan, Sri Lanka, Sudan, Swaziland, Syrian Arab Republic, Tajikistan, Tanzania, Thailand, Togo, Tonga, Tunisia, Turkmenista, Tuvalu, Uganda, Ukraine, Uzbekistan, Vanatu, Venezuela, Vietnam, West Bank and Gaza, Yemen, Zambia, Zimbabwe. *Contined on next page >*	Ministries of Health, non-governmental organisations, UN agencies, donor agencies (including agencies working on behalf of PEPFAR and the Global Fund).		Ex-works.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Incoterms for delivery of goods
ViiV (continued)	*...Contined* In the context of ViiV's licence agreement for Tivicay (dolutegravir) with the MPP in all least developed countries (LDC), Sub-Saharan Africa (SSA) and low income countries (LIC), 67 in total, ViiV Healthcare has adopted a slightly different pricing policy. In these regions, Tivicay (dolutegravir) is offered for a non-fixed at-cost price (based on volumes and distribution costs) as part of public market tenders until a generic product has received approval. In middle-income countries, ViiV provides a pricing policy for all their ARVs that factors in the gross domestic product (GDP) and the impact of the epidemic in each country to improve affordability. Therefore, in middle-income countries, pricing is on a **case-by-case basis**.	Ministries of Health, non-governmental organisations, UN agencies, donor agencies (including agencies working on behalf of PEPFAR and the Global Fund).		Ex-works.

ANNEX 3: COMPANY CONTACTS

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GLOSSARY AND ABBREVIATIONS

3TC: Lamivudine, a nucleoside analogue reverse transcriptase inhibitor.

ABC: Abacavir, a nucleoside analogue reverse transcriptase inhibitor.

AIDS: Acquired Immune Deficiency Syndrome.

ANVISA: Brazil's national health surveillance agency, responsible for approval and oversight of pharmaceutical products, medical devices, health services, food, cosmetics, and tobacco.

ARV: Antiretroviral; medicines that treat HIV/AIDS.

ART: Antiretroviral therapy; a combination of ARVs used to treat HIV/AIDS.

ATV, ATV/r: Atazanavir, an HIV protease inhibitor; atazanavir/ritonavir, a boosted HIV protease inhibitor.

AZT: Zidovudine, a nucleoside analogue reverse transcriptase inhibitor.

BMS: Bristol Myers-Squibb.

CAEME: Association of multinational pharmaceutical companies in Argentina.

Category 1: In this document, 'Category 1' refers to the countries that are eligible to receive the deepest discount on a company's ARV price.

Category 2: In this document, "Category 2' refers to countries that are not eligible for a company's deepest discount on ARV pricing, but are nevertheless offered a lesser discount.

DAAs: Direct-acting antivirals, oral drugs used to treat hepatitis C virus.

DRV, DRV/r: Darunavir, an HIV protease inhibitor; darunavir/ritonavir, a boosted HIV protease inhibitor.

DTG: Dolutegravir, an HIV integrase inhibitor.

DTI: Department of Trade and Industry.

EFV: Efavirenz, an HIV non-nucleoside reverse transcriptase inhibitor.

EMA: European Medicines Agency.

ETV: Etravirine, an HIV non-nucleoside reverse transcriptase inhibitor.

EU: European Union.

Evergreening: Making minor changes to medicines that are already on the market, to extend patents.

FTAs: Free trade agreements.

FTC: Emtricitabine; a nucleoside analogue reverse transcriptase inhibitor.

Generic drug: According to WHO, a generic drug is a pharmaceutical product that is usually intended to be interchangeable with the originator product.

GFATM: The Global Fund to Fight AIDS, Tuberculosis and Malaria.

GSK: GlaxoSmithKline.

HCV: Hepatitis C virus.

HIV: Human Immunodeficiency Virus.

IATT: IInter-Agency Task Teams on Children and HIV and AIDS.

INTERFARMA: The Pharmaceutical Research Industry Association; a multinational group of pharmaceutical companies located in Brazil.

IP: Intellectual property.

LDCs: Least-developed countries.

LPV/r: Lopinavir/ritonavir, a boosted HIV protease inhibitor.

MPP: Medicines Patent Pool.

MSF: Médecins Sans Frontières; Doctors Without Borders.

NDRA: National Drug Regulatory Authority.

PEPFAR: The President's Emergency Plan for AIDS Relief.

PI: Protease inhibitor.

PPPY: Per person, per year.

RAL: Raltegravir, an HIV integrase inhibitor.

RCEP: Regional Comprehensive Economic Partnership.

RTV or /r: Ritonavir, an HIV protease inhibitor used only at a low dose to boost levels of other HIV protease inhibitors.

SRA: Stringent regulatory authority.

TAF: Tenofovir alafenamide, a pro-drug of tenofovir.

TB: Tuberculosis.

TDF: Tenofovir; a nucleotide analogue reverse transcriptase inhibitor.

TPP: Trans-Pacific Partnership.

TRIPS: Trade-Related Aspects of Intellectual Property Rights.

UNAIDS: Joint United Nations Programme on HIV/AIDS.

UNITAID: a market-shaping institution that facilitates and accelerates availability of medicines and diagnostics for HIV/AIDS, tuberculosis, malaria and hepatitis C.

US: United States.

US FDA: United States Food and Drug Administration.

VL: Voluntary licence.

WHO: World Health Organization.

WTO: World Trade Organization.

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