UNTANGLING THE WEB OF

ANTIRETROVIRAL PRICE REDUCTIONS

17th Edition – July 2014

ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

www.msfaccess.org

PREFACE

This 17th edition of *Untangling the Web of Antiretroviral Price Reductions* is a departure from recent previous years. For this edition, the methods of collecting information on the sources and prices of antiretrovirals (ARVs) remain the same, but information is presented in a new, shorter format focusing on a few key drugs as well as future regimens, along with an analysis of the current opportunities, challenges and threats faced in keeping the price of ARVs down.

The Methodology, Pharmaceutical Company Contacts and Conditions of Offer, can all be found online at:

www.msfaccess.org/utw17

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.

www.msfaccess.org

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 currently provides HIV treatment in projects in 24 countries, implementing treatment strategies to reach more people, earlier in their disease progression, while increasingly encouraging patients to take on a more central role in the management of their care.

Over the past 14 years, the MSF Access Campaign has been monitoring the patent barriers, prices and availability of ARVs 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 decade, 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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INTRODUCTION

Today, nearly 12 million people are receiving lifesaving antiretroviral therapy (ART)[1], up from 9.7 million at the end of 2012. An additional 17 million people are eligible for ART[2], based on the 2013 World Health Organization (WHO) consolidated HIV treatment guidelines, which reflect mounting evidence that early treatment has significant benefits in reducing illness, death, and the risk of transmission.

Three years ago, the HPTN 052 study found that early initiation of HIV treatment helps prevent further transmission of the disease by up to 96%[3], bolstering the growing evidence that successful antiretroviral therapy (ART) is one of the most important prevention tools we have.[4]

Global efforts to scale-up ART are aimed at reaching as many people as possible, as early as possible, in order to help people suppress the virus (**see viral load box**, next page), thus helping to protect their immune system while dramatically reducing risk of HIV transmission. One of the key strategies to achieve viral suppression for a greater number of people is providing ART at the community level.

In Chiradzulu, Malawi, an MSF study found that a combination of strategies, including decentralised ART (through task shifting), viral load monitoring, and community-based ART support groups, helped achieve high adherence (91% of people on ART with a viral load below 1,000 copies/mL), as well as a low incidence of new infections in communities with high ART coverage.[5]

With more people on treatment than ever before, the remaining challenge of doubling the number of people reached who are eligible for ART means that the affordability of antiretroviral drugs (ARVs) remains a key concern for treatment scale-up, particularly for second-line and salvage regimen ARVs.

The prices of first-line regimens are continuing their decade-long downward trend – down from over US$10,000 per person per year (ppy) for first-line treatment in 2000 to around $140 ppy today for recommended regimens – thanks to generic competition enabled through a variety of strategies, including the use of legal flexibilities in international trade rules, known as TRIPS flexibilities, and the expiry of patents.[6]

Second-line medicines are now being produced in India by generic producers, after Indian civil society made significant efforts to file pre-grant oppositions challenging secondary patents.[7] But not all countries have access to these more affordable generic products. Some countries, including Thailand, Indonesia and Ecuador,[8] have issued compulsory licences to enable production or importation of generic versions of second-line drugs, while others continue to pay very high prices.

Third-line, or salvage-, regimens remain too expensive for most people and governments in developing countries, with some regimens priced nearly 15 times higher than first-line regimens. Patents on these newest drugs continue to block generic production and affordable access, and will do so for decades to come in some cases, unless governments, generic companies and civil society use the legal means at their disposal to encourage generic competition.

Countries classified as 'middle-income economies' face particularly steep challenges. Typically unable to access the lowest prices, despite 75% of the world's poor living in these countries, some middle-income countries are excluded from voluntary licence agreements pharmaceutical companies negotiate with the Medicines Patent Pool or bilaterally with generic manufacturers. Tiered pricing – where a company will try to maximise profits by setting different prices for the same product in different countries, based on economic status – is gaining favour with some of the world's biggest global health actors.[9] While tiered pricing has long been practised by the pharmaceutical industry, there is considerable concern that potential implementation of this strategy by some of the world's biggest procurers of medicines would entrench the practice and permanently leave middle-income countries at a disadvantage.

New threats are emerging that could keep the prices of ARVs higher for longer. Many countries face an escalating number of patents on ARVs due to TRIPS and TRIPS-plus measures, and out-dated laws or patent systems that facilitate so-called 'evergreening', or secondary patenting. Developing countries also face substantial bilateral pressure from industry and the governments of wealthy countries, including the United States, to abandon pro-public health intellectual property laws and efforts to promote generic competition. India in particular has recently come under close scrutiny from the US for its intellectual property rules, which were the subject of Congressional hearings and has been included once again in the US's 2014 Special 301 trade report. In South Africa, a scandal dubbed 'Pharmagate' exposed the

pharmaceutical industry's covert efforts to derail national patent law reform.[10]

Trade negotiations also place many countries under pressure. The attempted introduction of TRIPS-plus measures as part of trade negotiations is becoming common practice. The Trans-Pacific Partnership agreement (TPP) trade negotiations between the US and 11 other countries, including low- and middle-income countries across the Asia-Pacific Rim, could set a harsh new precedent for intellectual property provisions in a trade agreement, with severe consequences for access to medicines.[11]

The widespread lack of transparency on the prices paid by governments for medicines is also a serious issue and underscores the need for procurers and countries to publish prices. A good precedent has been set by countries who publish tenders and prices paid, as South Africa currently does,[12] in order to ensure that they are getting the best prices possible against an established regional benchmark.

VIRAL LOAD: BETTER TREATMENT MONITORING TO KEEP PEOPLE ON FIRST-LINE FOR LONGER

Viral load monitoring – measuring how many copies of HIV are in the blood as an indicator of how well the virus is being suppressed by ART – is the gold standard for monitoring treatment. While viral load testing is routine in wealthy countries, the cost and complexity of the tests have, until recently, been a barrier to scaling up in developing countries. This is changing, however, as new products – both laboratory-based and point-of-care – and new operational strategies to lower costs – such as using dried blood spots and ensuring high-throughput viral load machines are used at their full capacity – are introduced.

Data from an MSF study – presented in *How Low Can We Go*, a report which looks at the total costs of rolling out viral load in several countries – show that the biggest component of costs lie in reagents and consumables.

However, there was a large price range for reagents and consumables paid by different countries. A further MSF-supported study showed the cost of manufacture to be much lower than the price paid, and often by a significant margin.[13] The low cost of manufacture, paired with the variation in prices paid by countries, suggests that the price of viral load is flexible and can come down considerably with improved tendering and stronger price negotiation.

Driving down the cost of viral load monitoring to enable scale up in developing countries, along with the provision of adherence counselling and decentralised treatment, is critical to ensuring that people stay on first-line treatment for as long as possible. This is particularly critical as the switch from first- to second-line regimens more than doubles the prices paid for ARVs.

LINE BY LINE:
A LOOK AT THE REGIMENS

FIRST-LINE TREATMENT:
SMALL DECREASE IN PRICE; COUNTRIES MOVE TO TDF-BASED REGIMENS OVER AZT

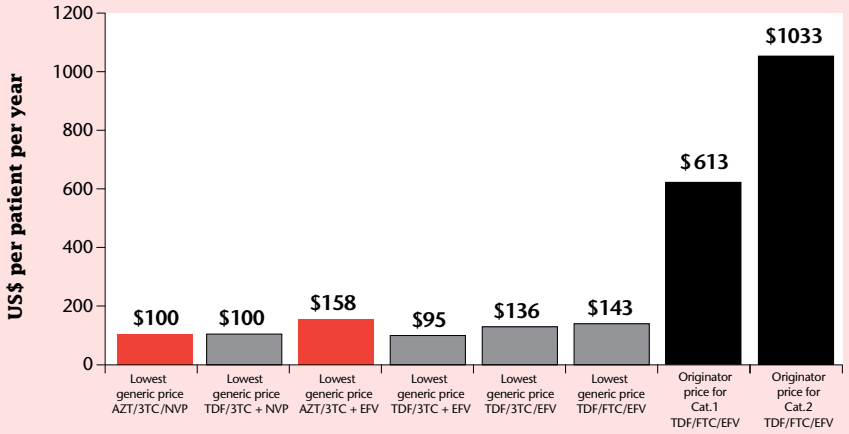
With 29 million people worldwide eligible to receive HIV treatment, price reductions in first-line regimens – however small – are critical to ensuring those who should receive treatment have affordable access to it.

The lowest price of the generic first-line one-pill-a-day combination tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) fell only slightly by around 2% last year, from US$139 ppy to $136 ppy, despite the recent introduction of two additional quality-assured sources, Aurobindo and Cipla – **see Graphs 1 and 2**. With two new sources, it is anticipated that increased competition will bring the price down further in the future. Competition among generic producers has seen the lowest price of stand-alone TDF fall by almost half in 12 months, from $48 ppy in 2013 to $26 ppy today.

Despite new quality-assured generic sources of medicines and the increase in competition, the price of originator sources of TDF-based one-pill-a-day regimens (TDF/FTC/EFV) has remained static for the last seven years, since 2007. Today, the lowest priced quality-assured generic source of the one-pill-a-day combination represents a 77% discount on the lowest priced originator one-pill-a-day combination.

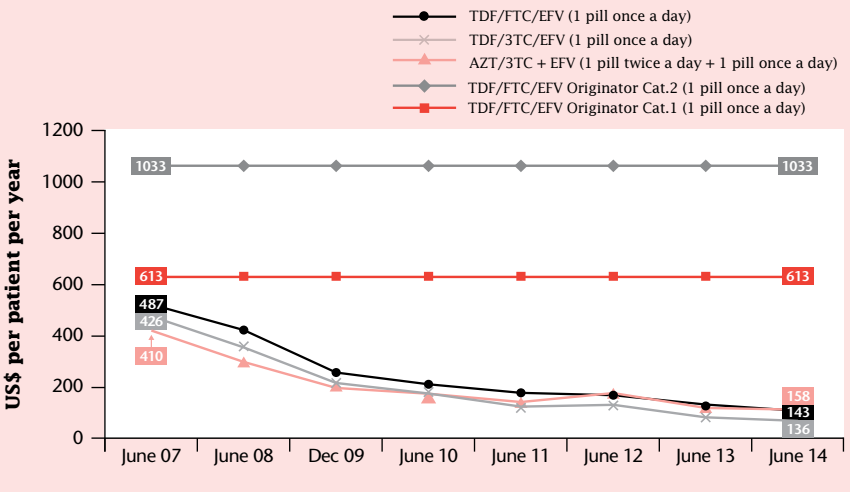
While options containing zidovudine (AZT) are cheaper – at $100 ppy – than those with TDF, TDF regimens are better tolerated by people, with fewer side effects, and can be taken once a day, meaning people are more likely to adhere to treatment. This is reflected in the move to TDF-based regimens over AZT-based ones as countries increasingly phase out stavudine (d4T).

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



*Disclaimer for TDF/3TC + EFV: this calculation is based on the sum of two products, whereas other prices were directly reported by manufacturers.

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



In 2012, it was estimated that nearly half of all adult patients on first-line treatment in countries with generic access were on TDF-based combinations. And by the end of 2014, it is estimated that as many as 70% of first-line patients in several countries – including South Africa, Zimbabwe and Zambia – will be receiving TDF-based regimens.[14]

Middle-income countries continue to be squeezed by high prices when there's not enough reliance on generic competition, with those countries falling under 'category 2' paying more than $1,000 ppy ($1,033 ppy) for TDF/FTC/EFV for the originator product. Some countries, however, are paying more than double for this combination, with Argentina paying $2,679 ppy and Mexico $2,391 ppy for TDF/FTC/EFV. In addition, many middle-income countries do not have triple fixed-dose combinations (FDCs) for first-line treatment; this lack of a one-pill-a-day option in these countries could hinder treatment scale up and adherence.

SECOND-LINE TREATMENT: NEW QUALITY-ASSURED SOURCES, AND GENERICS NOW CHEAPER, BUT MIDDLE-INCOME COUNTRIES CONTINUE TO PAY HIGH PRICES

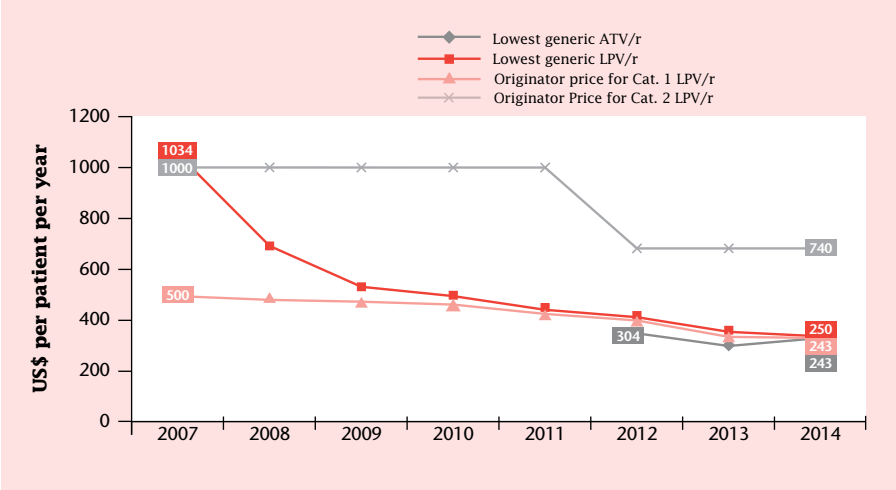
The prices of second-line regimens are increasingly important as more people need to switch to second-line therapy, especially those people identified through the increased use of viral load monitoring.

Protease inhibitors lopinavir/ritonavir (LPV/r) and atazanvir/ritonavir (ATV/r) have been recommended by WHO for second-line therapy.[15]

Although the cost of second-line combinations is still more than double the price of first-line regimens, the price of originator and most generic sources of second-line combinations continue to fall. While the lowest-priced originator source (AbbVie, formerly known as Abbott) of LPV/r fell a further 5.7% to $250 ppy, for the first time, a generic company – Mylan – has undercut the originator's price, reporting a lower price of $243 ppy, a decrease of 9.3% from last year **– see Graph 3.**

However, the price of Mylan's generic ATV/r, at $243 ppy, ticked up by nearly 11% this year, up from $219 ppy last year. A second generic source from Emcure was tentatively approved by the US Food and Drug Administration (USFDA) in February 2014, but no pricing information was provided for this report. With new quality-assured generic sources, and the Medicines Patent Pool striking a deal with Bristol-Myers Squibb to licence ATV in December 2013[16], increased competition should see the price of this combination fall in the coming years, although this may be slow because of remaining patent barriers for ritonavir.

GRAPH 3: THE EVOLUTION IN PRICE OF BOOSTED PROTEASE INHIBITORS FOR SECOND-LINE REGIMENS

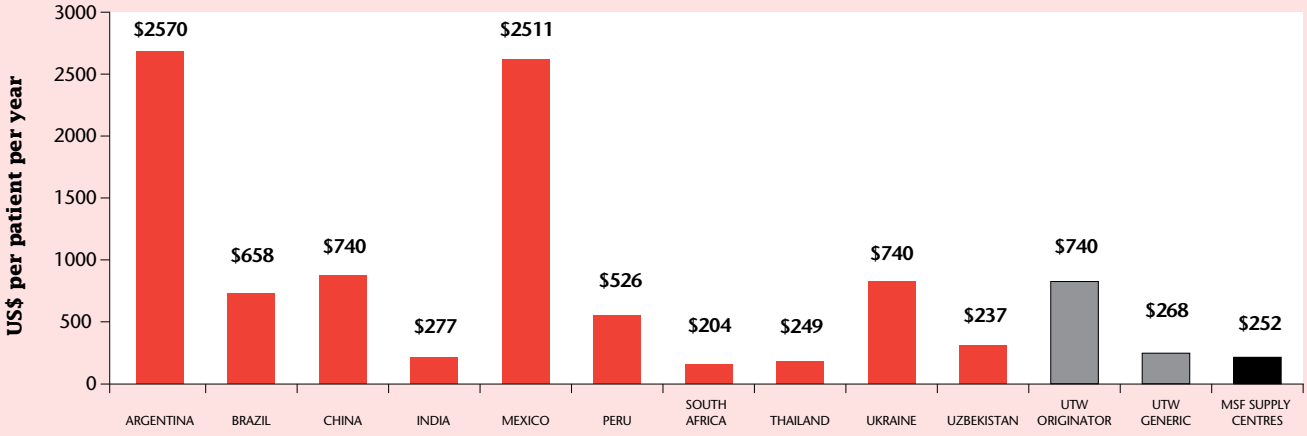


However, ATV/r represents only one in six protease inhibitors used in second-line treatment.[17] Although ATV/r can be dosed once daily and is generally better tolerated than LPV/r, countries have not made the move to switch to ATV/r despite these facts. The resulting low volumes may hinder a further reduction in prices.

Additional potential components of second-line regimens could include cobicistat and darunavir (DRV). Cobicistat, an investigational ARV booster currently under development, has been touted as a potential alternative to ritonavir.[26] A second-generation protease inhibitor, darunavir, boosted with RTV, could become part of standard second-line treatment as studies have shown it to be more effective than LPV/r,[27] and – as it has potential to be significantly dose-reduced – could be more affordable with fewer side effects **– see DRV Profile.**

Middle-income countries – especially those in Latin America – continue to pay exorbitant prices for LPV/r for use in second-line regimens, with Argentina ($2,570 ppy) and Mexico ($2,511 ppy) paying over 12 times more for LPV/r than South Africa ($204 ppy) **– see Graph 4.**

GRAPH 4: 2013 PRICE PER PATIENT PER YEAR LPV/R AS COMPONENT OF SECOND-LINE ARV REGIMEN



Sources: Argentina, Peru and Mexico: Antiretroviral Treatment in the Spotlight[28]; Thailand, Ukraine, Uzbekistan: The Global Fund Price and Quality Reporting[17]; Brazil, China, India, South Africa: responses to questionnaires sent from MSF to countries.

PAEDIATRICS: TREATMENT GAPS NEED TO BE CLOSED AS EARLY DIAGNOSIS AND ART ARE SCALED UP

Children living with HIV who start ART early – before 12 months of age – are more likely to have an undetectable viral load, have a smaller viral reservoir, and have better neurocognitive outcomes than those who start ART later in life.[18,19] These positive outcomes underscore the critical importance of diagnosing children early and getting them on effective, well-tolerated ART.

But gaps in the treatment of children remain. While there were 260,000 new paediatric infections of HIV in 2012 – down by 52% since 2001 – with 647,000 children under 15 years of age receiving ART in 2012, the coverage rate for children is only 34% – half the coverage rate of adults.[20]

Prices for paediatric formulations, especially generic ones, are trending down, with some formulations for lopinavir/ritonavir (LPV/r) and nevirapine (NVP) falling by 14% and 31% respectively, this year. Critically, new, better tolerated and easier to swallow paediatric formulations will soon be available **– see Lopinavir/ritonavir pellets Profile.**

Studies are also looking to new potential paediatric regimens, with dolutegravir (DTG) currently being assessed for safety and efficacy in treating children, while a granule formulation is also being developed.[21]

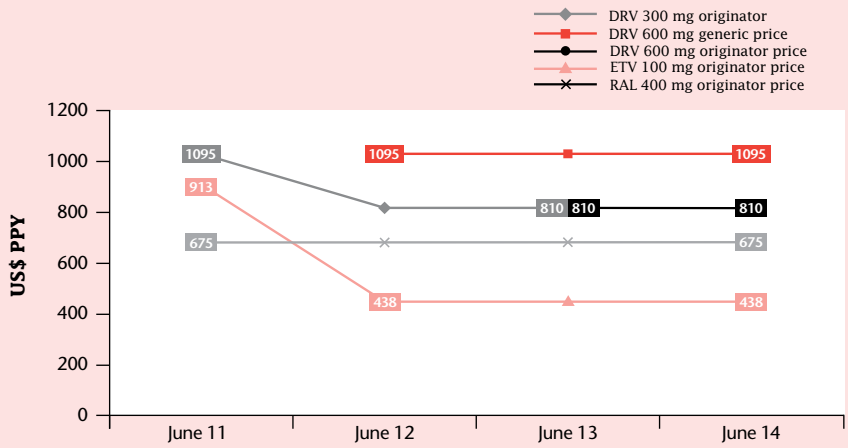
SALVAGE-LINE TREATMENT:
NEWEST DRUGS PRICED OUT OF REACH

There are no quality-assured generic versions of darunavir (DRV), etravirine (ETV) or raltegravir (RAL) **– see RAL Profile**. While the price of ETV has fallen by more than half (52%) since 2011 – from $913 ppy to $438 today – prices of other salvage-line drugs haven't changed in two years and they remain prohibitively expensive. The price of RAL has remained stagnant for three years at $675 ppy. While both the 300mg and 600mg dose of the originator DRV are priced at $810 ppy, the sole generic source of DRV 600mg (which is not stringent regulatory agency-approved) remains more expensive at $1,095 ppy **– see Graph 5.**

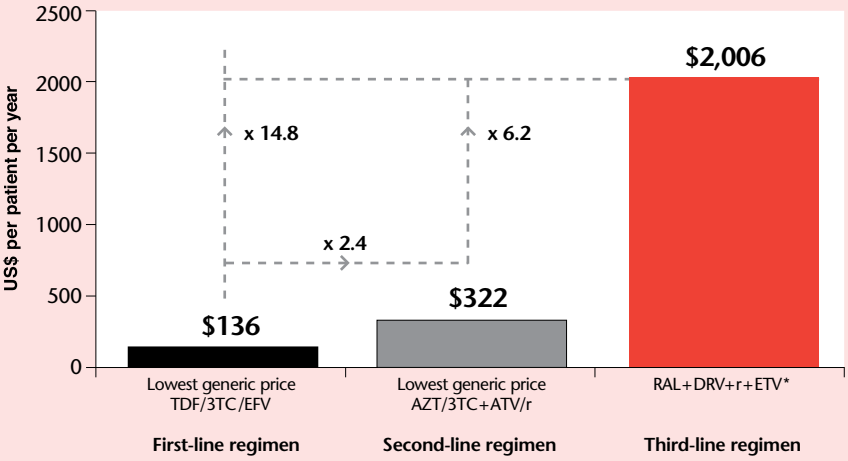
At $2,006 ppy, the best price for a third-line combination of RAL + DRV + r + ETV, salvage regimens remain nearly 15 times more expensive than first-line combinations and over six times more expensive than second-line treatment **– see Graph 6**. Middle-income countries, however, pay even more. For RAL – just one of the drugs needed in a multi-drug salvage regimen – Argentina pays $8,986 ppy, Peru $5,643, and Thailand $4,676 ppy; South Africa pays $617 ppy **– see Graph 7.**

The astronomically high prices of salvage-line drugs in many of these countries is due to extensive patent protection – in India, patents on RAL won't expire before 2022[36] and the lack of open generic competition is a barrier to scaling up use of salvage therapies as medical needs expand.

GRAPH 5: THIRD-LINE ARV PRICE REGIMENS

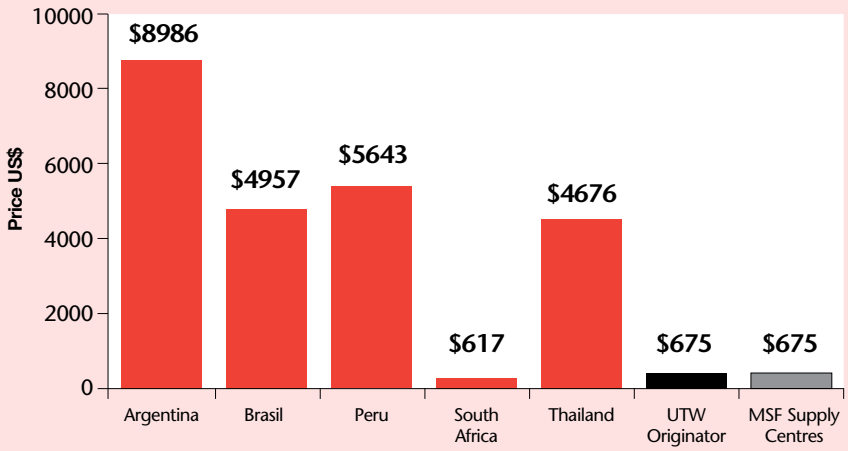


GRAPH 6: PRICE COMPARISON OF TREATMENT REGIMENS



*Note: The price of the third-line ARV regimen of US$2,006 was calculated by adding the three individual prices of the originator product.

GRAPH 7: 2013 PRICE PER PATIENT PER YEAR RAL



Sources: Argentina, Peru and Mexico: Antiretroviral Treatment in the Spotlight[28]; Thailand, Ukraine, Uzbekistan: The Global Fund Price and Quality Reporting[17]; Brazil, China, India, South Africa: responses to questionnaires sent from MSF to countries.

LOOKING TO THE FUTURE: NEW DRUGS, NEW REGIMENS

As people living with HIV live longer, and resistance to existing drugs and regimens develops, the need for new drugs and regimens – and the optimal combinations and sequencing of drugs – will be critical. Additional studies are needed, but there are promising signs.

Existing drugs such as darunavir – **see DRV Profile** – and efavirenz (EFV) could also play roles in future standard regimens. DRV could become part of standard second-line therapy in the future, with studies showing it to be more effective than LPV/r. Reducing the dose of EFV to 400mg from 600mg may help to reduce side effects, improve adherence[40] and the success of EFV-based therapy, as well as reduce cost. But questions remain as to whether this lower dose formulation will remain robust for patients on first-line tuberculosis therapy and for pregnant women.

However, new drugs and those that will soon emerge from the pipeline are those that show the most promise. Dolutegravir (DTG) – **see DTG Profile** – has shown to be very promising in first-line regimens, but more data is needed. Clinical trial data has shown that ABC/3TC/DTG is superior to recommended first-line regimen TDF/FTC/EFV in achieving virologic suppression and control.[41] A study which will compare DTG head to head against EFV 400mg is being planned, and studies on the use of DTG in women of childbearing age and people co-infected with tuberculosis are already underway.[42, 43] Integrase inhibitors such as DTG are an important new class of drug to provide stronger regimens and additional options for patients; of this class, DTG seems to have the most promise and benefits, and its development and access should be prioritised.

From the pipeline, tenofovir alafenamide (TAF) – **see TAF Profile** – a pro-drug of tenofovir, has been shown to be very effective with fewer side effects than TDF, including causing fewer kidney problems. Promisingly, TAF has shown to be just as effective as TDF while containing less of the active ingredient - a potentially price-lowering innovation.[44] TAF is being co-formulated with emtricitabine, elvitegravir and cobicistat and is in phase III trials now.[45]

Other pipeline drugs also show promise. A new class of drugs, attachment inhibitors, are being tested with the first in this class, BMS-663068, recently undergoing a dose-finding study that revealed significant decrease in viral load.[46] Doravirine is a new NNRTI which has demonstrated favourable potency when compared with EFV and potentially has a better side effect profile. This drug also seems to be effective at a low dose (25mg) and therefore may be inexpensive to produce.[47]

Induction-maintenance strategies are also being investigated. This strategy aims to get a patient to an undetectable level of viral load with one regimen and then, once undetectable, switches to a simpler or potentially more affordable regimen to maintain viral suppression. A Phase IIb study using pipeline oral drug GSK-744 in combination with oral rilpivirine (RPV) in people already with an undetectable viral load showed that 82% of patients remained undetectable, against 71% of those taking EFV in combination with two NRTI drugs.[48] Another study is being planned for induction with oral medicines and then maintenance with long-acting injectable formulations of GSK-744 and rilpivirine.

POLICY: THREATS AND OPPORTUNITIES FOR AFFORDABILITY

Countries are being asked to step up and implement the latest WHO guidelines, but expensive medicines continue to be an obstacle to further scale-up. Developing countries – and especially middle-income countries – continue to be challenged by policies that threaten to overwhelm their ability to purchase affordable medicines. Free trade agreements, bilateral pressure from wealthy countries, particularly from the United States and the European Union, a lack of transparency from pharmaceutical companies, and abusive patenting practices: these measures are leaving developing countries increasingly on the back foot in a bid to ensure they can afford the medicines needed by their populations.

But some countries are undertaking proactive strategies to overcome these obstacles. South Africa and Brazil are moving towards patent law reform that would tighten the requirements for pharmaceutical patents to be granted. With millions of more people now eligible to receive HIV treatment – and people increasingly needing to switch to more expensive second- and salvage-line regimens – the need for open, transparent policies that allow the cost of ARVs to come down has never been more critical.

FOLLOWING INDIA: PATH TO PROGRESS OR PRESSURE?

On the back of several landmark events in India – including the Supreme Court finally rejecting Novartis' challenge to its patentability criteria, and the grant of the country's first compulsory licence – several middle-income countries are looking to India's lead for accessing affordable medicines for their own use. Countries including South Africa, Brazil, Indonesia, Argentina and Peru are looking to India's experience of using TRIPS flexibilities, including pre-grant patent examination and third party oppositions, compulsory licences, and laws to stop abusive patenting, including evergreening.

South Africa is currently reforming its patent law, which is outdated and has a significant adverse impact on the affordability and accessibility of new medicines. Patents in South Africa are granted without substantive review, and the country fails to stop pharmaceutical companies from evergreening, which leads to an excessive amount of pharmaceutical patents; in 2008 alone, South Africa granted 2,442 patents on pharmaceuticals, compared to just 278 in Brazil over a five-year period from 2003 to 2008.[62] Up to 80% of these pharmaceutical patents might not have been granted if patent applications were reviewed.[63]

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Furthermore, South Africa has not employed existing measures such as issuing compulsory licences to bring down the price of patented drugs that are too expensive for those who need them.

With an estimated 5.6 million people living with HIV, South Africa may find it difficult to access affordable second- and salvage-line treatments, or promising new first-line treatments, if national laws do not take full advantage of TRIPS flexibilities to reduce prices. In September 2013, the South African Department of Trade and Industry released the long-anticipated Draft National Policy on Intellectual Property (DNPIP), which indicated that the government plans to make a number of changes to the country's patent laws to better incorporate TRIPS flexibilities.[64] The policy calls most notably for the establishment of a patent examination system, coupled with stricter criteria for granting a patent, and the establishment of patent opposition procedures.[65] But the reforms have met with fierce resistance from the multinational pharmaceutical industry, and in January 2014, leaked documents revealed a Big Pharma strategy to delay reform of the national IP policy, inclusive of TRIPS flexibilities.[66]

Brazil is also moving toward reforming its patent laws. In 2013, legislators released a report which compiled strong evidence on the need for reform of Brazil's patent law and the need to explore alternative mechanisms to promote medical research that responds to priority health needs.[67] Several legislative bills – dating from between 1999 and April 2013 – have been tabled in the Brazilian parliament aiming to reform Brazilian patent law and ensure it is better suited to answer public health needs. All of these bills are now attached to one bill that is slated to be discussed at the Constitution and Justice Commissio of the Brazilian National Congress.

If approved, the reform will improve public participation in the patent examination process, reinforce the rejection of frivolous patents, involve the health sector in the review patentability criteria, define better grounds to address abuses in monopolies, and ensure that generic competition starts as soon as a patent monopoly ends.

But countries following India's lead in using TRIPS flexibilities to prevent patent abuse should be aware that these measures are not without their risks.

India has issued just one compulsory licence, for the cancer drug sorafenib tosylate in 2012, which brought prices down dramatically through generic competition. In a significant development, an expert Indian government committee is compiling a list of patented drugs that may be prioritised for additional compulsory licences.[68] However, strong resistance to the Indian government employing additional compulsory licences – from wealthy country governments and multinational pharmaceutical companies – is expected in the months and years ahead and such pressure should not be underestimated.[69] With new drugs emerging from the pipeline under patent – now that the effects of India's 2005 patent reform are starting to have an impact – India will need to consider strong actions to ensure affordability of ARVs and other medicines.

India's policies and laws encourage strict patent examination, third party patent oppositions and other public health flexibilities, but India is under increasing pressure from wealthy countries, especially the United States, to bring its patent laws into line with US norms.

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The US pharmaceutical industry lobbied the US Trade Representative to label India a 'Priority Foreign Country' – reserved for countries who are seen to be the most serious infringers of intellectual property – on the US's Special 301 Trade List.[84] While India ultimately remained on the less severe Priority Watch List, there is powerful pressure being exerted to get India to conform to US intellectual property standards. This friction resulted in India's patent law safeguards and judicial decisions being questioned at several forums, including a US Congressional Hearing in 2013.[70] India has consistently stated that it will not consider diluting its patent law safeguards or domestic policies, which are fully TRIPS-compliant, and may even consider challenging the US in multilateral dispute resolution forums if the US chooses to impose trade sanctions.

India is on the cusp of tremendous changes in its pharmaceutical sector and the ability of its generic industry to produce medicines for developing countries. The catalyst for these changes is related to the 2005 patent law amendments, when India was obliged to introduce product patents on medicines. MSF was relieved at the inclusion of public health safeguards in India's new patent law, but warned that these would only protect access to medicines in the short term. In the long term, new patented drugs, particularly those developed in this century, may be much more difficult to move into generic production, leading to steep prices for new medicines, including ARVs.

MSF will continue documenting the impact of India's Patent Act on the prices of medicines, while working with others to ensure that the mechanisms and provisions allowed for in the law are fully implemented, to ensure the widest possible access to affordable life-saving medicines both in India and beyond.

STUCK IN THE MIDDLE: WHY MIDDLE-INCOME COUNTRIES ARE PAYING THE PRICE

Middle-income countries (MICs), where as many as three-quarters of the world's poor live, are increasingly the targets of policies designed to extract maximum profits from these markets. These include policies being pushed by pharmaceutical firms, trade negotiators, and now, global health actors that result in a lack of price transparency and more challenges in accessing affordable medicines.

This policy landscape is reflected in the high prices many MICs are paying for ARVs, including China, Peru, Uzbekistan, Mexico, Brazil and Argentina. The price paid for lopinavir/ritonavir for second-line treatment in Argentina ($2,570 ppy)[28] and Mexico ($2,511) is more than 12 times the price paid in South Africa ($204 ppy). Ukraine ($740 ppy), Brazil ($658 ppy) and China all pay similarly high prices[17, 71] – **see Graph 4.**

The reasons behind why some MICs pay more or less than others vary as much as the prices. Some countries have used TRIPS flexibilities to greater effect than others, resulting in lower prices. For example, India has not granted secondary patents for a majority of ARVs and thereby has secured production by generic producers. Thailand, which pays $249 ppy for LPV/r as a component of second-line regimens, issued a compulsory licence for this drug in 2007.[72]

In South Africa, following complaints lodged by the Treatment Action Campaign that GlaxoSmithKline and Boehringer Ingelheim (BI) were charging excessively high prices for patented ARVs, the Competition Commission[73] in December 2003

required both companies to licence the products to generic companies on the grounds that GSK and BI had abused their dominant positions in the South African ARV market.

Since then, patent-holding companies have routinely included South Africa in the geographical scope of the licences they voluntarily negotiate with the Medicines Patent Pool (MPP) or generic companies directly. This enables the South African government to import and distribute generic ARVs in their HIV programme, despite a large number of ARV patents granted in the country.[52]

Brazil has instead opted to sign bilateral voluntary licences with companies for ARV production, which often results in prices that are more expensive than what generic competition could achieve, and is routinely excluded from MPP licences.

Transparency of prices – or, more often, the lack of it – also plays a key factor in price for many countries. In the absence of credible information on prices being paid in other countries, ministries of health are often left with fewer choices and higher prices for drugs. Often increased transparency increases bargaining power of governments. South Africa, which has access to some of the most affordable ARVs, publicly discloses the prices it pays via public tender documents.[12]

Some countries are better at negotiating prices than others, but as companies and most countries don't disclose prices paid, governments are forced to negotiate on a case-by-case basis, without a benchmark to judge if they're getting a good deal. Ultimately, governments and procurers of drugs should publish the prices they're paying in a bid to open up price transparency and lower costs.

Lack of transparency also is a key concern with voluntary licences signed outside the Medicines Patent Pool. These licences often cannot be evaluated properly because of confidentiality agreements around the full terms and conditions. Pharmaceutical companies often highlight their voluntary licences as corporate social responsibility projects. Despite efforts to develop goodwill around voluntary licences, pharmaceutical companies ultimately don't disclose details that could shed light on the real impact of these licences.[74]

In February 2014, Indian generic drug manufacturer Cipla and multinational company Merck announced an India-specific partnership under which Cipla will have a non-exclusive licence to market, promote and distribute Merck's raltegravir under its own brand name.[75] This deal may have been signed by Merck to counter an ongoing push for a compulsory licence in India to lower the price of RAL. The deal between Merck and Cipla is a disappointment because it does not enable generic competition among multiple producers that could lead to dramatic price reductions.

The impact of voluntary licences signed by Brazil is also cause for serious concern. Brazil has chosen to focus on developing partnerships with originator companies through voluntary licences, with the goal of technology transfer and the development of local manufacturing capacity. However, the impact of this policy on access to medicines remains to be seen. A technology transfer agreement signed between the government of Brazil and Bristol-Myers Squibb for the local production of atazanavir, for example, is not expected to lead to significant price reductions or to improve the

ability to develop combinations that include atazanavir.[76]

Tiered pricing - where a company will set different prices for the same product in different countries – has long been a strategy pursued by pharmaceutical companies in a bid maximise profits in middle-income countries. But tiered pricing is less effective at lowering drug prices when compared to generic competition, including for ARVs.

A review of 7,000 developing country ARV purchases from 2002-2007 found that tiered prices were up to nearly 500% higher than generic prices.[77] Another analysis found that, comparing tiered prices with generic prices, 90% of products reviewed were more affordable as generic versions. Efforts by some global health actors to institutionalise tiered pricing policies as a solution to accessing affordable prices have been successfully challenged. Their efforts should be redirected towards fostering robust generic competition wherever possible.

TRADE POLICIES REMAIN A DANGER

Trade agreements and policies are a continued cause for concern. The Trans-Pacific Partnership Agreement (TPP), under negotiation between the United States and 11 other Pacific Rim countries, poses a significant threat to access to medicines and health, setting new and restrictive standards for intellectual property (IP) across Asia and the Americas that would dramatically expand monopoly protection for medicines and restrict the availability of price-lowering generic competition.

The trade pact would mandate data exclusivity for all drugs, including for biologic products, the lowering of patentability criteria to enable secondary patenting, and the creation of special investor rights under an Investor-State Dispute Settlement (ISDS) mechanism that would allow pharmaceutical companies and other corporations to sue governments via secret arbitration for public health regulations or legal safeguards that may limit anticipated pharmaceutical profits, including patent rejections and invalidations.

Although the US has recently proposed so-called 'differential treatment' that would allow certain TPP countries to be exempted from implementing some of the harmful IP provisions for a limited time, other provisions which would be immediately introduced still go beyond what is required of countries under existing international IP and trade rules. Time limits in the US proposal mean that, eventually, all TPP countries will have to implement provisions that would reduce access to affordable medicines.

The US has also indicated that the standards established under the TPP will be the template for future trade agreements, which could include countries that produce affordable generic medicines or have sizeable populations of people living with HIV.

Free Trade Agreements (FTA) from the European Union (EU) are also a cause for concern in developing countries. EU-India FTA negotiations, especially on intellectual property, are expected to resume in 2014 after elections in both the EU and India. The EU includes some of the most problematic intellectual property provisions in its negotiations, including data exclusivity, patent term extensions and a range of intellectual property enforcement provisions. An ISDS mechanism is also included in the proposed investment chapter of the EU-India FTA.

ISDS provisions in bilateral investment treaties (BITs), or as part of the investment chapters in FTA negotiations, can have negative impacts upon access to medicines.[78] Of particular note is a dispute brought by the US-based pharmaceutical company Eli Lilly against the Canadian government after an independent judicial authority in Canada invalidated frivolous secondary patent claims for two medicines.[79] Eli Lilly has filed a claim for $500 million as compensation from the Canadian government by applying the ISDS clause that was introduced under the North American Free Trade Agreement (NAFTA). The company's so-called investor-state challenge "marks the first attempt by a patent-holding pharmaceutical corporation to use the ISDS provision provided under 'trade' agreements as a tool to push for greater monopoly patent protections".[80] The case is an example of how investor protection clauses are being used to undermine the legitimacy of domestic policies and discretion of judicial authorities over national patent laws. Recently, some countries, including Indonesia and South Africa,[81] have started to take proactive steps to either terminate or review bilateral investment treaties that were previously signed. Such cases are leading to greater scrutiny of ISDS provisions in other trade negotiations such as the EU-India FTA and the TPP negotiations.

While the EU-India Free Trade Agreement negotiations have stalled due to elections for both governments in 2014, the EU has nonetheless enforced a revised customs regulation[82] which might still potentially allow the wrongful seizure of generic medicines in transit. This updated regulation replaced a previous one which had led to the seizure and detention of nearly 20 shipments of generic medicines.[83] Despite some very modest improvements, the new regulation does not address concerns raised by civil society and others, with many of the previous provisions that enable customs officials to mistakenly seize generic medicines remaining in place.

DARUNAVIR (DRV)

2013 WHO Guidelines

Boosted DRV is indicated as an option for third-line treatment regimens.[15]

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2014) are in **bold**.

	Daily dose	Janssen	Hetero
DRV 300mg tablet	4**	**810 (0.555)**	
DRV 400mg tablet	2*		730 (1.000)
DRV 600mg tablet	2**	**810 (1.110)**	1095 (1.500)

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

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

SPOTLIGHT ON ACCESS ISSUES

Darunavir (DRV) is already an important part of salvage-line therapy as it often maintains activity despite previous protease inhibitor (PI) exposure.[29,30,31,32] However, it has also been shown to be superior to LPV/r in patients who have not yet had exposure to a protease inhibitor.[27] Further, several studies suggest that lower doses of DRV can be used in patients who have not taken a PI before.[31,32,33] If further trials prove that dose-reduced DRV is equally effective in PI-naïve patients, lower doses may be used, thus possibly decreasing price. As darunavir can be given once daily in PI-naïve patients, is relatively well tolerated and has potential for dose and price reduction, it may be considered as an important option for second-line therapy, but this will depend on the supply and price.

Currently, Janssen (a pharmaceutical company of Johnson & Johnson) has the only quality assured-source, but Hetero in India is also manufacturing the 400mg and 600mg version of the tablets. They have submitted both formulations to the US FDA for review and approval is expected by the end of 2014. Hetero offers a more affordable pricing option if the order is for a full batch size, as compared to ordering less than the standard batch size.

Patents

The basic patent was applied for by Searle and Monsanto in August 1993 and expired in 2013. Subsequently, US National Institutes of Health (NIH) and the University of Illinois applied for patents related to DRV in 1999 and licensed the patents to Tibotec (today part of Janssen/Johnson & Johnson) for development. Tibotec later applied for patents related to different forms and combinations of DRV.

Between 1998 and 2004, Tibotec filed a number of secondary (evergreening) patent applications.[34] The application for a patent on the base compound was not filed in India but nevertheless, a series of evergreening applications filed by Tibotec on different forms and combinations of DRV were pending before the Indian patent offices, which if granted would have given Johnson & Johnson a monopoly for 24 years in India. All secondary patent applications in India were subsequently rejected after pre-grant oppositions, which encouraged generic producers to enter the market and start the process to quality-assure their formulations. As darunavir's importance in treatment guidelines and use grows, other developing countries will need to address high prices and barriers to generic competition, including patents.

In September 2010, the NIH licensed a patent on DRV to the Medicines Patent Pool (MPP), with all developing countries being covered in the geographic scope of the licence. However, the NIH patent will not enable generic competition in developing countries unless additional patents being held by Janssen are entered into the MPP.

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. The newly developed combination was submitted for US FDA approval in 2014.

In November 2012, Johnson & Johnson announced their intention not to enforce patents in sub-Saharan Africa and in least-developed countries.[35] However, this policy deliberately excludes patients living in developing countries considered to be 'middle-income' economies but where the needs are equally as important given the burden of HIV.

DOLUTEGRAVIR (DTG)

2013 WHO Guidelines

Not yet included. Approved by US FDA in August 2013 and by European Medicines Agency (EMA) in January 2014.

PRICE INFORMATION

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

SPOTLIGHT ON ACCESS ISSUES

Dolutegravir (DTG), a member of the integrase inhibitor class, is a key new drug which has been shown to be more effective in achieving virologic control as compared to current first-line TDF/FTC/EFV.[49] DTG is well-tolerated, effective, can be taken once daily, and has a high barrier to developing resistance. It is currently being studied in paediatric formulations including granule and dispersible formulations. Further, animal studies have shown no risk for birth defects and so far, no risk has been identified to human pregnancies. Given these characteristics, DTG is a good candidate for inclusion in first- or second-line treatment. Although additional studies are needed to determine if the optimal use of DTG is appropriate for initial treatment of HIV in low- and middle-income countries, dolutegravir will be a critical drug to improve HIV treatment. It is currently recommended as part of a first-line treatment option in the US.[50] However, in order to best assess if DTG or dose-reduced EFV is best fit for future first-line therapy globally, a study that compares TDF/FTC/EFV 400mg versus TDF/FTC/DTG is being planned. However, this study is not fully funded and has not started. Such research is critical to ensure that patients living in low- and middle-income countries get the best therapy.

Patents

Patents on the base compound of DTG were granted in many countries such as China, Indonesia and South Africa, and are pending examination in other countries including India, Brazil, Russia, and Egypt. In India, the base compound patent (if granted) will not expire before 2026.

On the base compound, Shionogi has also made use of special "Markush" patent claims; these enable the firm to seek a patent on several thousand molecules under a single application, thereby potentially inhibiting research and development on DTG and other integrase inhibitors which may belong to the same family of molecules.[51] In response, the Delhi Network of Positive People filed a pre-grant opposition in India in February 2013 against the grant of the Markush patent structure. GSK (founder of ViiV Healthcare with Pfizer in 2009) subsequently narrowed and amended its claims. The matter is still pending.

Manufacturer ViiV Healthcare and Shionogi (part owner of ViiV) have filed multiple secondary patents on DTG including multiple patents covering its intermediates and combinations.[52] Secondary patents will not expire before 2029.

On 1 April, 2014, the Medicines Patent Pool and ViiV Healthcare announced a licence agreement comprised of two voluntary licences on patents related to a paediatric formulation of dolutegravir, and a further voluntary licence for the adult formulation of DTG, including in combination with abacavir (ABC).[53] The licence uses a hybrid royalty structure. While the paediatric licence agreement is royalty-free in 121 countries, the adult licence – in addition to a geographic scope of 67 low-income countries that is royalty-free – includes six additional middle-income countries: Egypt, India, Indonesia, Philippines, Turkmenistan and Vietnam, offering a sliding royalty scheme based on per capita income. While both the public and private markets are included in the 67 countries designated as royalty-free for the adult formulation, the tiered royalty rate in the six additional countries only applies to the public market. The licence excludes certain MICs including Brazil and China, and for countries that are not covered by the licence and have no patent in force – such as Argentina and Venezuela – access to adult DTG is uncertain, subject to pending patent applications, subsequent patent applications for other combinations that may become preferred treatment options, and other barriers such as data exclusivity that would preclude registration of generic versions.

LOPINAVIR/RITONAVIR PELLETS (PAEDIATRIC FORMULATION) – LPV/R

2013 WHO Guidelines

LPV/r is recommended for first-line treatment for all HIV-infected children below three years of age (36 months), regardless of NNRTI exposure. LPV/r is also indicated for second-line treatment for children who receive an NNRTI for first-line.[15]

PRICE INFORMATION

No price information available

SPOTLIGHT ON ACCESS ISSUES

Paediatrics

Current WHO guidelines recommend initiation of a boosted protease inhibitor for all children younger than three years of age, as many children will be exposed to an NNRTI as part of Prevention of Mother-to-Child Transmission (PMTCT). Children are more likely to become undetectable and less likely to die if given LVP/r-based therapy over nevirapine (NVP)-based therapy.[22,23] However, the syrup formulation of LVP/r traditionally given to children has many issues, including a need for refrigeration, a very unpleasant taste, and a significantly high alcohol content.

A new pellet formulation of LPV/r[24] which can be mixed in food or milk has been developed and may be better tolerated and easier to administer for children – helping to improve adherence for paediatric patients, and ease the task of administering the medicine for care givers. In a recent study, the pellets were preferred over syrup by children who could not yet swallow tablets and their caregivers.[25] Manufactured by Cipla in India, with US FDA approval expected before the end of 2014, the pellets are heat stable, alcohol free, but not taste masked.

Patents

Most patents related to ritonavir (RTV) could also cover LPV/r paediatric formulations and could block access to this lifesaving formulation for infants and children. A thorough analysis is needed to reveal how patents could block access in developing countries.

RALTEGRAVIR (RAL)

2013 WHO Guidelines

RAL is indicated as an option for third-line treatment regimens.[15]

PRICE INFORMATION

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

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution.
Products quality-assured by US FDA or WHO prequalification (as of May 2014) are in bold.

	Daily dose	Merck		Hetero
		Category 1 countries	Category 2 countries	
RAL 400mg tablet	2	**675 (0.925)**	**Case-by-case basis**	1752 (2.400)

SPOTLIGHT ON ACCESS ISSUES

Raltegravir (RAL) is an integrase inhibitor – a new class of drugs which have a novel mechanism of action and no apparent cross resistance with other classes of ARVs – which has been used very little in low- and middle-income countries; transmitted drug resistance in these countries is negligible. RAL is indicated as an option for adults and children over two years of age who are failing second-line treatment. This drug has been shown to be non-inferior to efavirenz (EFV) in treatment naïve patients, and effective as a component of regimens for treatment-experienced patients.[37]

However, it has some barriers to its use as part of a public health approach to HIV care; RAL is dosed twice daily, has relatively frequent adverse events of liver inflammation, has a low barrier to resistance, and must be dose-adjusted in patients on first-line tuberculosis treatment. Further, it is not currently routinely recommended for use in pregnant women, with some treatment-related birth defects noted in animal studies.[37]

Merck, the innovator company, currently has the only quality-assured source, but Hetero in India is also manufacturing the 400mg tablet, which was submitted to the US FDA for review and approval is expected by the end of 2014. Hetero offers a more affordable pricing option for their product if the order is for a full batch size, as compared to ordering less than the standard batch size.

Patents

The Institute for Research in Molecular Biology (IRBM), one of Merck's research sites, applied for the basic patent on RAL in October 2002, which is due to expire in 2022. In 2005, Merck and IRBM applied for a patent on the potassium salt of RAL which can run up to 2025.

Merck and IRBM applied for international patent applications under the Patent Cooperation Treaty (PCT) which facilitated the filing of these applications in many PCT member states, including some developing countries with generic drug manufacturing capacity like Brazil, China, India and South Africa.

In India, IRBM was granted a patent in December 2007 which will not expire until 2022.[36] An application on the potassium salt of RAL is also pending for review before the Indian patent office[38] and a pre-grant opposition was filed in August 2013 by Delhi Network of Positive People. Nevertheless, the basic patent is a barrier for generic production, even for domestic use.

Merck has segmented the market and charges much higher prices for RAL in some Latin American countries, especially compared to India or South Africa. Merck has refused to licence RAL to the Medicines Patent Pool and signed voluntary licences with two generic companies, Emcure and Mylan, in 2011 to supply RAL to only 60 sub-Saharan African and low-income countries.[39] Significantly, although the voluntary licences were granted to Indian generic companies to produce and export RAL, India itself is excluded from the licences' geographical scope. RAL produced locally by the licencees cannot be marketed in India.In February 2014, Indian generic drug manufacturer Cipla and multinational company Merck announced an India-specific partnership under which Cipla will have a non-exclusive licence to market, promote and distribute Merck's raltegravir under its own brand name.

With a limited number of developing countries within the geographical scope of the licences, patients and governments in middle-income countries are deliberately excluded from benefiting from generic competition from India, with the result that many countries are paying high prices – Argentina pays $8,986 ppy, Peru $5,643, and Thailand $4,676 ppy.

TENOFOVIR ALAFENAMIDE (TAF)

2013 WHO Guidelines

Not yet included. Starting Phase III clinical trials.

PRICE INFORMATION

Prices not yet available; generic versions are not yet available

SPOTLIGHT ON ACCESS ISSUES

Tenofovir alafenamide (TAF), a pro-drug of TDF, has been shown to be very effective with fewer side effects. While TDF currently forms the backbone of preferred first-line regimens and is effective, safe and well-tolerated for most patients, side effects can be a problem for others. TDF may cause kidney damage for patients with pre-existing risk factors such as those with poorly-controlled diabetes. However, several studies have shown that TAF is less likely to cause kidney problems and does not cause as much bone demineralisation as TDF. As TAF concentrates extremely well inside cells but does not have very high levels in the plasma, it means that each pill can contain less of the active ingredient but be just as effective – a potentially price-lowering innovation. TAF is being co-formulated with emtricitabine (FTC), elvitegravir and cobicistat and is being trialled in phase III now. In order for TAF to reach its full impact, registration that includes flexibility in its use and ability to be combined with other ARVs is required. As such, TAF should be registered as a single drug.

Patents

The basic patent of TAF was first applied for in the US by Gilead in 2000.[54] The patent has been granted in a number of middle-income countries including India, China and South Africa, and will expire between 2021 and 2023 in those countries.[55,56,57] Preliminary information on the secondary patents relating to TAF indicates that Gilead has filed for a patent on a combination with FTC in the US and other countries such as China and Mexico,[58] the equivalent of which has already been rejected in India.[59]

Little is known about the cost of the Gilead product or the cost of the active pharmaceutical ingredients. Once TAF is approved by stringent regulatory authorities, it is inevitable that treatment programmes will seek more affordable generic versions, and will look to India as a source. However, a patent blocks generic companies from marketing or exporting generic versions until July 2021, even if they receive approval from the Indian Drug Regulatory Authority and the WHO pre-qualification programme.[52]

In India, Gilead has also filed a series of divisional applications – i.e. applications that contain matter from a previously filed application (so-called parent application) – in an attempt to entrench its patent monopoly. If Gilead's granted patent for TAF were to be challenged and revoked, Gilead could still revive its claims through divisional patent applications.[60]

No generic versions of TAF currently exist, but Gilead is in closed-door negotiations with Indian generic companies for bilateral voluntary licences. Gilead is also in negotiations with the Medicines Patent Pool to licence TAF, however no final agreement had been reached at time of publication.[61]

ANNEX 1: SUMMARY TABLE OF ALL PRICES

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

The price in brackets corresponds to the price of one unit (tablet, capsule, etc.).

Products included in the WHO List of Prequalified Medicinal Products (as of May 2014) are in **bold**.

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies								
Abacavir (ABC)		ViiV		Aurobindo	Cipla	Hetero	Mylan					
20mg/ml oral solution	12ml	**340 (0.078)**		**237 (0.054)**	**183 (0.042)**	**158 (0.036)**						
60mg tablet	4				**122 (0.083)**		**128 (0.088)**					
Atazanavir (ATV)		Bristol-Myers Squibb (BMS)		Emcure	Mylan	Strides						
		Category 1 countries	Category 2 countries									
100mg capsule	xx			**(0.267)**								
150mg capsule	2	**412 (0.564)**	**412 (0.564)**	**268 (0.367)**								
200mg capsule	xx	**(0.677)**	**(0.677)**	**(0.483)**								
300mg capsule	1			**268 (0.733)**	**183 (0.500)**	128 (0.350)						
Atazanavir/ ritonavir (ATV/r)				Hetero	Mylan							
300/100mg tablet	1			256 (0.700)	**243 (0.667)**							
Darunavir (DRV)		Janssen		Hetero								
300mg tablet	4	**810 (0.555)**										
400mg tablet	2			730 (1.000)								
600mg tablet	2	**810 (1.110)**		1095 (1.500)								
Efavirenz (EFV)		Merck		Aurobindo	Cipla	Emcure	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides
		Category 1 countries	Category 2 countries									
30mg/ml suspension	xx	**(0.094)**	**case-by-case basis**									
50mg capsule	xx			**(0.075)**				**(0.067)**				
50mg tablet	xx	**(0.114)**	**case-by-case basis**									
100mg dispersible tablet	xx										**(0.106)**	
200mg capsule	3			**77 (0.070)**	**67 (0.061)**			**58 (0.053)**			**61 (0.056)**	
200mg tablet	3	**394 (0.360)**	**case-by-case basis**						**55 (0.050)**			**113 (0.103)**
600mg tablet	1	**237 (0.650)**	**case-by-case basis**	**40 (0.110)**	**55 (0.150)**	**61 (0.167)**	**47 (0.130)**	**38 (0.103)**	**49 (0.133)**	**73 (0.200)**	**44 (0.120)**	**41 (0.112)**
Emtricitabine (FTC)				Cipla								
200mg capsule	1			**61 (0.167)**								
Etravirine (ETV)		**Janssen**										
100mg tablet	4	**438 (0.300)**										
Lamivudine (3TC)		**ViiV**		Alkem	Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy	Strides	
10mg/ml oral suspension	10ml	**184 (0.050)**			**28 (0.008)**	**30 (0.008)**	**37 (0.010)**					
150mg tablet	2	**75 (0.103)**		**44 (0.060)**	**27 (0.037)**	**30 (0.042)**	**26 (0.036)**	**24 (0.033)**	**29 (0.040)**	**24 (0.033)**	**28 (0.038)**	
300mg tablet	1					**37 (0.100)**	**14 (0.039)**	**24 (0.067)**				

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies									
Lopinavir/ ritonavir (LPV/r)		Abbvie		Aurobindo	Cipla	Hetero	Mylan						
		Category 1 countries	Category 2 countries										
80/20mg/ml oral solution	4ml	**150 (0.103)**	**296 (0.203)**		**256 (0.175)**								
100/25mg heat-stable tablet	3	**108 (0.099)**	**278 (0.254)**	**150 (0.137)**									
200/50mg heat-stable tablet	4	**250 (0.171)**	**740 (0.507)**	**268 (0.183)**	**304 (0.208)**	**304 (0.208)**	**243 (0.167)**						
Nevirapine (NVP)		Boehringer Ingelheim		Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Quality Chemicals	Ranbaxy	Strides		
		Category 1 countries	Category 2 countries										
10mg/ml suspension	20ml	**380 (0.052)**	**532 (0.073)**	**61 (0.008)**	**61 (0.008)**								
50mg tablet for oral suspension	4			**75 (0.052)**	**43 (0.029)**								
200mg capsule	2												
200mg tablet	2	**219 (0.300)**	**438 (0.600)**	**28 (0.038)**	**32 (0.044)**	**32 (0.044)**	**26 (0.036)**	**29 (0.040)**	**41 (0.056)**	**29 (0.040)**	**29 (0.040)**		
Raltegravir (RAL)		Merck		**Hetero**									
		Category 1 countries	Category 2 countries										
400mg tablet	2	**675 (0.925)**	**Case-by-case basis**	1752 (2.400)									
Ritonavir (RTV)		Abbvie		Hetero	Mylan								
		Category 1 countries	Category 2 countries										
80mg/ml oral solution	xx	**(0.091)**	**Case-by-case basis**										
100mg heat-stable tablet	2	**83 (0.114)**	**Case-by-case basis**	183 (0.250)	**177 (0.243)**								
Tenofovir (TDF)		Gilead		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy	Strides				
		Category 1 countries	**Category 2 countries**										
300mg tablet	1	**207 (0.567)**	**365 (1.000)**	**55 (0.150)**	**49 (0.133)**	**48 (0.132)**	**49 (0.133)**	**51 (0.140)**	**26 (0.071)**				
Zidovudine (AZT)		ViiV		Aurobindo	Cipla	Hetero	Micro Labs	Mylan	Ranbaxy				
10mg/ml oral solution	24ml	**395 (0.045)**		**91 (0.010)**		**100 (0.011)**							
60mg tablet	4						**44 (0.030)**						
100mg capsule	xx	**(0.092)**		**(0.046)**	**(0.055)**								
100 mg tablet	xx												
250mg capsule	xx	**(0.320)**											
300mg tablet	2			**73 (0.100)**	**73 (0.100)**	**79 (0.108)**	**70 (0.096)**	**79 (0.108)**	**69 (0.094)**				

ARVs in alphabetical order	Daily dose	Originator companies		Generic companies								
ABC/3TC		ViiV		Aurobindo	Cipla	Mylan						
60/30mg tablet	4			**229 (0.157)**	**146 (0.100)**	**96 (0.066)**						
600/300mg tablet	1	**234 (0.640)**		**219 (0.600)**	**176 (0.483)**	**164 (0.450)**						
d4T/3TC				Cipla	Hetero	Ranbaxy	Strides					
6/30mg dispersible tablet	4			**49 (0.033)**								
12/60mg dispersible tablet	2			**40 (0.055)**								
30/150mg tablet	2			**43 (0.058)**	**39 (0.053)**	**40 (0.054)**	**38 (0.052)**					
d4T/3TC/NVP				Cipla	Hetero	Ranbaxy	Strides					
6/30/50mg dispersible tablet	4			**57 (0.039)**								
12/60/100mg dispersible tablet	2			**52 (0.072)**								
30/150/200mg tablet	2			**58 (0.080)**	**59 (0.081)**	**62 (0.085)**	**58 (0.079)**					
TDF/FTC		Gilead		Aurobindo	Cipla	Hetero	Mylan	Strides				
		Category 1 countries	Category 2 countries									
300/200mg tablet	1	**319 (0.875)**	**548 (1.500)**	**74 (0.203)**	**85 (0.233)**	**79 (0.217)**	**71 (0.193)**	**80 (0.219)**				
TDF/FTC/EFV		Merck		Aurobindo	Cipla	Hetero	Mylan	Ranbaxy				
		Category 1 countries	Category 2 countries									
300/200/600mg tablet	1	**613 (1.680)**	**1033 (2.830)**	**146 (0.400)**	**152 (0.417)**	**143 (0.392)**	**143 (0.392)**	164 (0.450)				
TDF/3TC				Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy			
300/300mg tablet	1			**57 (0.155)**	**73 (0.200)**	**64 (0.177)**	**63 (0.173)**	**106 (0.291)**	**62 (0.170)**			
TDF/3TC/EFV				Aurobindo	Cipla	Hetero	Mylan					
300/300/600mg tablet	1			**140 (0.383)**	**140 (0.383)**	**139 (0.382)**	**136 (0.372)**					
TDF/3TC+NVP (co-pack)				Hetero	Mylan							
300/300 + 200mg co-pack	1 kit (3 tabs)			**122 (0.333)**	**100 (0.275)**							
AZT/3TC		ViiV		Aurobindo	Cipla	Hetero	Microlabs	Mylan	Quality Chemicals	Ranbaxy	Strides	Univ. Corp
60/30mg tablet	4				**56 (0.038)**			**48 (0.033)**		**56 (0.038)**		
300/150mg tablet	2	**169 (0.232)**		**101 (0.138)**	**85 (0.117)**	**93 (0.128)**	**82 (0.113)**	**79 (0.108)**	**116 (0.158)**	**81 (0.111)**	**80 (0.110)**	**106 (0.145)**
AZT/3TC/ABC				Strides								
60/30/60mg tablet	3			**73 (0.067)**								
AZT/3TC/NVP				Aurobindo	Cipla	Hetero	Mylan	Quality Chemicals	Ranbaxy	Strides		
60/30/50mg tablet	4				**110 (0.075)**		**88 (0.060)**					
300/150/200mg tablet	2			**100 (0.137)**	**106 (0.146)**	**110 (0.150)**	**100 (0.137)**	**145 (0.198)**	**102 (0.139)**	**103 (0.142)**		
AZT/3TC + EFV (co-pack)				Aurobindo	Hetero	Ranbaxy	Strides					
300/150 + 600mg tablets (co-packs)	1 kit (3 tabs)			**158 (0.433)**	225 (0.617)	**219 (0.600)**	**170 (0.467)**					

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GLOSSARY AND ABBREVIATIONS

3TC: Lamivudine; nucleoside analogue reverse transcriptase inhibitor.

ABC: Abacavir; nucleoside analogue reverse transcriptase inhibitor.

ATV: Atazanavir, protease inhibitor.

ATV/r: Atazanavir/ritonavir; boosted protease inhibitor.

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

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

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

COBI: Cobicistat; a drug currently in development used to increase the levels of elvitegravir and, possibly, HIV protease inhibitors, to allow for lower and fewer doses of these medications while maintaining effectiveness.

d4T: Stavudine; nucleoside analogue reverse transcriptase inhibitor.

Data exclusivity: The period during which the data of the original marketing authorisation holder relating to (pre-) clinical testing is protected. During this time, the generic applicant may not refer to the information of the original marketing authorisation holder before filing their applications for marketing authorisation.

DRV: Darunavir, protease inhibitor.

DRV/r: Darunavir/ritonavir; boosted protease inhibitor.

DTG: Dolutegravir; new integrase inhibitor submitted for US FDA approval in 2013.

EFV: Efavirenz; non-nucleoside analogue reverse transcriptase inhibitor.

ETV: Etravirine; non-nucleoside reverse transcriptase inhibitor.

FDC: Fixed-dose combination – multiple drugs combined in a single pill.

FTC: Emtricitabine; nucleoside analogue reverse transcriptase inhibitor.

Generic: A generic drug is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference (originator) medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated. A generic company sells generic medicines.

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

MPP: Medicines Patent Pool. The Pool's mission is to bring down the prices of HIV medicines and facilitate development of better-adapted HIV medicines, such as simplified fixed-dose combinations and special formulations for children, by creating a pool of relevant patents for licensing to generic manufacturers and product development partnerships.

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor.

NRTI: Nucleoside Analogue Reverse Transcriptase Inhibitor.

NtRTI: Nucleotide Reverse Transcriptase Inhibitor.

NVP: Nevirapine; non-nucleoside analogue reverse transcriptase inhibitor.

Originator: An originator drug is a novel drug that was under patent protection when launched onto the market. An originator company is a company that sells originator medicines.

Patent: Patents are awarded to pharmaceutical companies when they develop a new drug. The patent grants that company the right to exclusively make, use and sell that drug for 20 years. It stops generic companies from making the drug and means the originator company can charge high prices without other companies undercutting them. The most effective and sustainable way to reduce the price of a drug is competition, but patents block other producers from entering the market.

Patent opposition: A mechanism that can be used to ensure that drug patents are not granted frivolously, whereby a person, nongovernmental organisation (NGO), lawyer, health organisation, researcher or market competitor opposes a patent application, whether it has already been granted (postgrant opposition) or is still under analysis by a patent office (pre-grant opposition). Patent oppositions are a key way to protect public health interests.

PPY: Per patient per year.

Prequalification: More commonly known as WHO Prequalification, the WHO List of Prequalified Medicinal Products was initiated by WHO and developed in collaboration with other UN organisations, principally for procurement by UN agencies. The project evaluates pharmaceutical manufacturers and products according to WHO-recommended standards of quality and compliance with Good Manufacturing Practices. WHO's Prequalification Programme is a benchmark for the identification of quality essential medicines and has significantly improved access to quality medicines over the past years.

Pro-drug: A pro-drug is a medication that is administered as an inactive (or less than fully active) chemical derivative that is subsequently converted to an active pharmacological agent in the body, often through normal metabolic processes. A pro-drug serves as a type of precursor to the intended drug.

R (or RTV): Low-dose ritonavir, used as a booster.

RAL: Raltegravir; integrase inhibitor.

RIL (or RPV): Rilpivirine, (TMC 278), Non-Nucleoside Reverse Transcriptase Inhibitor.

RTV: Ritonavir; protease inhibitor.

SRA: Stringent drug regulatory authority. A drug regulatory authority which is (a) a member of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, or ICH; or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein.

TAF: Tenofovir alafenamide; nucleotide reverse transcriptase inhibitor and pro-drug or precursor drug to tenofovir.

TDF: Tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

TPP: Trans-Pacific Partnership Agreement, a free trade agreement currently under negotiation between Australia, Brunei, Chile, Canada, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the US and Vietnam.

TRIPS: Trade-related Aspects of Intellectual Property Rights.US FDA: United States Food and Drug Administration.

ViiV: Joint venture created in 2010 by GlaxoSmithKline, Pfizer and Shionogi focusing on the R&D and commercialisation of HIV medicines.

Viral load: HIV viral load measures the level of HIV in the blood. Effective HIV treatment should result in a very low (or 'undetectable') viral load.

ACKNOWLEDGEMENTS:

Front cover photo:
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Back cover photo:
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Design/artwork/print:
ACW Ltd
+44 (0)20 8392 4330
www.acw.uk.com

The editorial team wishes to thank Margot TM Reinders for her help in preparing the data.

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