



DECISIONS AROUND HIV TREATMENT IN 2015: SEVEN WAYS TO FAIL, DERAIL OR PREVAIL

Fifteen years after antiretroviral therapy (ART) was first provided to people in developing countries in the public sector, 15 million people are receiving treatment (as of March 2015) – a significant global accomplishment that meets the goals of the 2011 UN High Level Meeting on HIV/AIDS agreed upon by all member states.

However, this represents less than half the number of people who will be eligible for ART once WHO recommends treatment for all people living with HIV – currently 36.9 million people. Furthermore, less than a quarter of children living with HIV are getting the treatment they need.

UNAIDS has set ambitious goals for 2020: 90% of people living with HIV will know their status; 90% of all people diagnosed with HIV will receive ART; and 90% of all people receiving ART will reach and maintain viral suppression.¹

While Médecins Sans Frontières (MSF) welcomes these new targets, we are also confronted with the shortcomings of the global HIV response on a daily basis. In several countries where we work, treatment access is severely limited, such as in the Democratic Republic of Congo, where only 17% of people have access to treatment.²

Meeting the UNAIDS 90/90/90 goals – and ensuring the rapid scale-up that

is needed to get as many people as possible on life-saving treatment – will be challenging. Success will rely in large part on use of the most robust and affordable treatment regimens, as well as on mobilising the political and financial support for the full package of medicines, treatment monitoring and adherence support needed to help people achieve and maintain ‘undetectable’ levels of virus.



IN THIS ISSUE BRIEF:

We first review trends in generic competition and intellectual property (IP) licensing for key antiretroviral drugs.

We then outline seven momentous decisions to be made in 2015 that will largely determine whether ART will be affordable, available and robust for the next 15 years of treatment scale-up to all people living with HIV.

This includes opportunities for greatly improved treatment regimens based

on WHO guidelines on when to start treatment, and what first- and second-line regimens should include.

We review threats and opportunities relating to efforts to secure affordable access to ART in the future, including potential decisions over the next year on India’s regulatory and IP laws and policies, on IP provisions proposed in the Trans-Pacific Partnership (TPP) trade agreement, on the response of the Global Fund to Fight AIDS, Tuberculosis and Malaria (‘Global Fund’) to antiretroviral (ARV)

market challenges and funding eligibility, and on the World Trade Organization (WTO) Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) Council’s consideration of the proposed TRIPS waiver extension on pharmaceuticals for least developed countries (LDCs).

Finally, we take stock of the current state of the ARV market with a snapshot of ARV prices for select second- and third-line ARV medicines by originator and generic manufacturers.



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TRENDS IN GENERIC COMPETITION AND IP LICENSING

When ART was first introduced in developing countries, treatment cost more than US\$10,000 per person per year (ppy). Thanks to competition among generic manufacturers, primarily in India, the most affordable quality-assured first-line regimen today costs \$116 ppy.³ However, newer medicines that are more efficacious and better tolerated are not priced as affordably. In some cases, patent barriers prevent the production or importation of generic versions of those medicines. Governments must make full use of flexibilities to overcome patent barriers and high prices in the coming year.

Recent developments in voluntary licensing between originator companies and the Medicines Patent Pool (MPP) for key ARVs indicate a trend towards better terms and conditions, but further improvements are still required. For example, expanding the geographic scope of voluntary licences to include additional middle-income countries, and ensuring licensees can sell generic versions to excluded countries that have not issued competition-blocking patents. Compulsory licensing remains an important and underutilised policy tool to ensure access for countries deliberately excluded from voluntary licences.

VOLUNTARY LICENCES WITH THE MPP

The MPP has adopted new approaches in recent voluntary licence agreements,

as seen in licences signed with originators for dolutegravir (DTG), tenofovir alafenamide fumarate (TAF), paediatric lopinavir/ritonavir (LPV/r) and ritonavir (RTV). Some of these approaches improve upon past agreement terms, whereas others present opportunities for further improvement. For example, the MPP voluntary licence with Viiv Healthcare for the adult formulation of DTG includes a few middle-income countries (MICs), but imposes tiered royalties based upon economic indicators. While tiered royalties may enable inclusion of some additional MICs into voluntary licences, since many MICs are increasingly viewed as key commercial markets by pharmaceutical companies, tiered royalties may prove to be only a limited solution that does not address the broader trend of exclusion of MICs from voluntary licences.

Furthermore, using economic indicators to expand the geographic scope of voluntary licences could leave behind marginalised and poor people living in certain MICs. These countries are home to large numbers of people living with HIV, but face reduced donor support, increasingly strict IP rules and high prices charged by multinational companies for patented products. MICs, even with an expanded geographic scope, may be left behind due to use of economic indicators that do not take into account underlying poverty, disease burden and lack of access to medicines. Alongside efforts to expand access in MICs via improved licences and use of TRIPS flexibilities (especially compulsory licensing), more effort is also needed to address regulatory barriers for registering generic medicines in countries both included and excluded from voluntary licences.

SPOTLIGHT ON TAF LICENCE WITH THE MPP

The Gilead licence for TAF signed with the MPP offers incremental improvements upon earlier MPP agreements with Gilead. Since the licence agreement was signed prior to the completion of TAF's marketing approval and market entry, generic companies did not need to wait until the originator product was on the market before developing generic versions. This may help accelerate the development and registration of generics. The TAF licence also opens the possibility for generic sub-licences and active pharmaceutical

ingredient (API) suppliers not only in India, but also in China and South Africa, to produce generic TAF, tenofovir disoproxil fumarate (TDF) and cobicistat (COBI). It further opens the possibility for these generic producers to export to other countries covered under the licence.

However, the TAF licence also presents some points of concern. Many countries are excluded from the benefits of generics under the terms of this licence, including MICs like Brazil, Colombia, Ukraine

and China – even though Chinese generic companies can develop TAF, TDF and COBI for export. Finally, excluding generic companies and API suppliers in countries other than China, South Africa and India from sub-licensing also limits global generic competition. Countries excluded from the voluntary licence should address access concerns by considering compulsory licences while also proactively engaging the MPP and patent holders on the terms and conditions of the voluntary licences.

COMPULSORY LICENCES

As IP barriers persist, use of compulsory licences remains a critical legal strategy to facilitate access to affordable ARV medicines. Recent compulsory licensing campaign efforts in Colombia have made remarkable progress and similar efforts have been adopted in Peru.

In Colombia, a compulsory licence campaign was started to trigger the reduction of the price of LPV/r.⁴ Civil society organisations in Peru have similarly submitted requests for issuing a compulsory licence on atazanavir since 2014.^{5,6}

DARUNAVIR: TRENDING IN THE WRONG DIRECTION

The darunavir (DRV) patent holder, pharmaceutical company Janssen, has still not yet concluded a voluntary licence with the MPP on DRV, including for paediatric populations.⁷ Instead, Janssen is carrying out confidential bilateral negotiations for a voluntary licence that covers only 59 countries. Janssen and Tibotec (now Janssen Therapeutics) have filed a range of secondary patents for DRV around the world.⁸ These secondary patents have led to an extension of patent protection on DRV until 2025 in South Africa and also in other MICs such as Mexico and China.⁸

Janssen's donation programme for paediatric tablet formulations of DRV (and etravirine, ETV) has resulted in only three countries taking part due to restrictive and onerous requirements.⁹ Donations are not sustainable for ensuring access to treatment and are difficult for countries to manage effectively. Such programmes also undermine long-term efforts to create sustainable approaches, such as applying 'push' and 'pull' incentives for companies and other entities to develop, market and deliver paediatric formulations of new and existing medicines.



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⁹ This includes requirements that the country must be a LDC in sub-Saharan Africa, have third-line treatment available for adults and have approved the products for paediatric use in the country. For more information, see: <http://www.pedaids.org/pages/treatmentdonation>.

SEVEN DECISIONS IN 2015 THAT WILL DRIVE OR UNDERMINE THE GLOBAL HIV RESPONSE

❖ 1. WHO: Recommend immediate treatment for all people living with HIV, or retain less ambitious guidelines?

In 2015, WHO will release new HIV treatment guidelines that will offer recommendations on when to start treatment. WHO should take into account available new evidence in revising these recommendations. In 2011, the HIV Prevention Trials Network's HPTN 052 trial results showed that early ART not only keeps people alive, but also dramatically reduces (by 96%) the likelihood of the virus being transmitted sexually.¹⁰ Furthermore, in 2015, the Strategic Timing of Antiretroviral Treatment (START) trial results showed that the benefits of starting treatment immediately after diagnosis far outweigh waiting until a person's immune system begins to deteriorate.¹¹ These studies strongly support a move towards providing all people living with HIV with treatment, regardless of the state of their immune system. Offering treatment upon diagnosis could help prevent unnecessary sickness and reduce loss to follow up among pre-ART patients. MSF's multi-centric retrospective cohort analysis over 10 years indicated that among more than 30,000 people living with HIV enrolled in pre-ART and not eligible for ART under WHO guidelines, 31% were lost to follow up.¹²

❖ 2. WHO: Revise ARV treatment regimen guidelines, or miss the opportunity to improve tolerability and efficacy?

A MORE ROBUST

FIRST-LINE REGIMEN:

Today's first-line regimen of tenofovir/ (emtricitabine or lamivudine)/ efavirenz (TDF/XTC/EFV) is effective and relatively well tolerated, with evidence that more than 90% of people in clinical trials remain on EFV-based first-line ART after an average of 78 weeks.¹³ The one-pill-a-day dosing of this combination eases the burden on people, and the regimen can be used for those also on tuberculosis (TB) treatment, pregnant women and children as young as three.¹⁴ At less than \$120 ppy, it is also an affordable regimen.

But can we do better? One option for improving first-line treatment in the near term is to use DTG instead of EFV. DTG has significant potential advantages over today's first-line ART: DTG has shown superiority over multiple first-line treatment options in getting people to undetectable faster (24 days, instead of 84 days with EFV) and keeping them there.^{15,16,17} This offers the additional benefit of preventing transmission, particularly in the contexts of sero-discordant couples and using ART for prevention of mother-to-child transmission (PMTCT). DTG is also better tolerated compared to an EFV-based first-line regimen¹⁸ and has a very high barrier to resistance.

The Clinton Health Access Initiative (CHAI) estimates that if DTG were sequenced into first-line ART, after several years of increasing volumes, the DTG price could be as low as \$32.50 per person per year, which

is lower than the \$45 ppy for EFV (600mg).¹⁹ However, such price reductions will only be available where there is generic competition, which is limited due to patents on DTG and a voluntary licence that covers only 73 low- and middle-income countries. Where patent barriers exist, prices will remain artificially high.

Following an agreement signed with ViiV Healthcare and CHAI, the Indian manufacturer Aurobindo submitted an application for the first generic DTG²⁰ to the US Food and Drug Administration (US FDA) in May 2015 for tentative approval. Scale-up through multiple suppliers will be needed to get to volumes that will allow eventual price reductions and cost savings, and national governments, donors and other stakeholders will need to support a rapid and safe transition.

With more people likely to be starting treatment even earlier in their disease progression, and therefore needing to be on treatment longer overall, it is crucial that WHO and national programmes ensure the best-tolerated and most-robust regimens are used in first-line ART. If DTG is proven to be safe and effective for pregnant women and in people co-infected with TB, moving it to first-line ART may provide significant advantages.

IMPROVING SECOND-LINE TREATMENT:

As viral load testing is scaled up in developing countries, more people with treatment failure are being identified and starting second-line ART. Today's most widely used second-line protease inhibitor backbone is lopinavir/ritonavir (LPV/r). However,

this drug has a number of drawbacks, including a high pill burden, twice-daily dosing, and frequent gastrointestinal side effects.

Atazanavir/ritonavir (ATV/r), which is now recommended as an alternative to LPV/r, has several advantages to support a change as a preferred choice for second-line regimens. ATV/r requires only once-daily dosing, offers better tolerability and is available at the same price as LPV/r. Competition has helped bring prices down to the point that today the most affordable WHO-prequalified version of ATV/r is priced at \$243 ppy – the same price as for LPV/r.

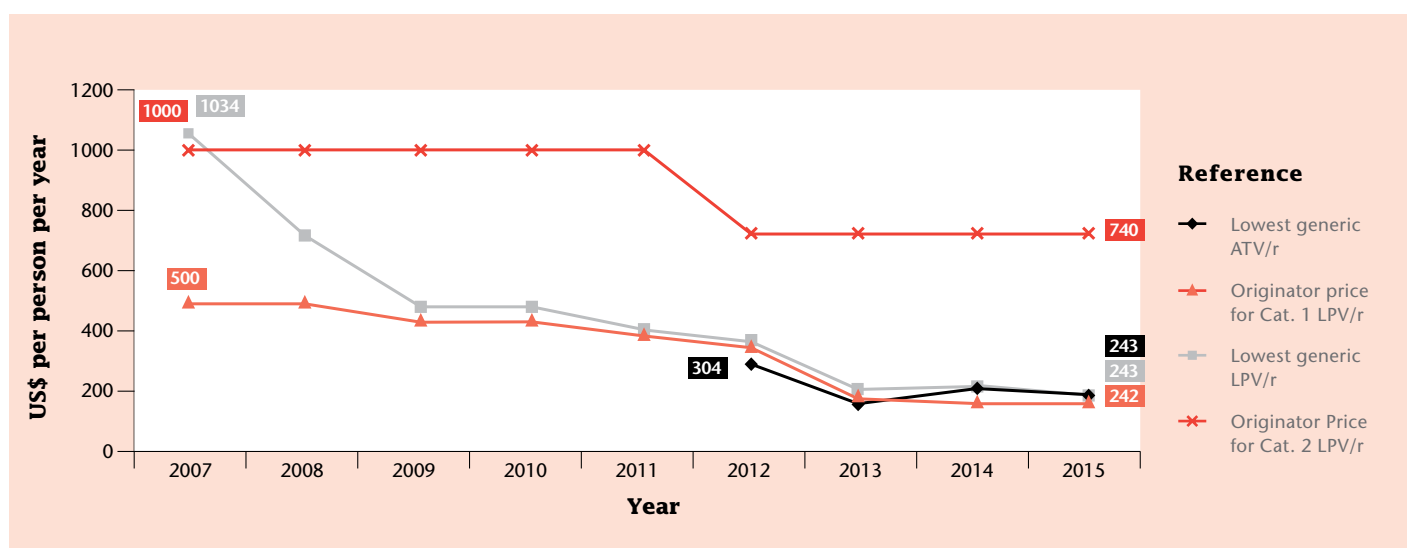
While the most affordable quality-assured generic LPV/r is priced at \$243 ppy, the originator product (from AbbVie) is consistently priced just below this, at \$242 ppy. This has led to the AbbVie product dominating the market, which carries significant risks associated with single-source

supply, such as stock outs, especially in a context where the demand is growing [See box on page 6]. For many countries that face patent barriers and are not eligible to access the lowest-priced product, the only option is AbbVie and the price can be up to 68% higher, at \$740 ppy [See Graph 1]. Use of ATV/r in second-line regimens is still limited, but increased demand should enable a more robust supplier base.

Another option for second-line regimens is to use darunavir/ritonavir (DRV/r). Today used primarily for salvage therapy, DRV/r offers specific benefits over the current standard LPV/r second-line therapy, including once-daily dosing, an improved side effects profile, a higher barrier to resistance, and improved efficacy as compared to LPV/r.²¹ However, one study in West Africa did not show increased efficacy using DRV/r compared to LPV/r in second-line therapy.²²

Unfortunately, DRV/r is still expensive. With original patents expiring in some countries where secondary patents were either rejected or not filed, generic manufacturers should be able to enter the market and eventually bring down prices. Early dose-ranging studies with DRV suggest that reducing the dose from 800mg to 400mg daily (with RTV) may have similar efficacy and may be better tolerated. The results of these studies may enable a dose reduction, as well as potential co-formulations with other ARVs²³ and possibly a role in second-line.¹⁹ Increased generic competition and the dose reduction could offer significant cost savings to developing countries where patents are not a barrier. Fixed-dose combinations (FDCs) of DRV/r are also in the pipeline.

GRAPH 1: THE EVOLUTION IN PRICE OF BOOSTED PROTEASE INHIBITORS FOR SECOND-LINE REGIMENS



SOUTH AFRICA: SINGLE SOURCE SUPPLIERS & SHORTAGES

Pharmaceutical company AbbVie is the patent holder and only supplier of LPV/r in South Africa. Since early 2015 there have been concerns of shortages and, in some regions of the country, even stock outs of LPV/r products.^b This is due in part to longer international lead times from AbbVie to supply the product, and in part to poor supply chain management at some locations in-country. While South Africa is included in a voluntary licence between Abbvie and MPP for two specific paediatric formulations (liquid suspension and 40mg/10mg pellet), no generic versions are marketed in South Africa yet. Furthermore, patents on LPV/r are still enforced in South Africa and – barring action by the government or other third party to overcome IP barriers – could block generic entry of other paediatric and adult formulations until 2024 and 2026. For example, a third paediatric formulation, a 100mg/25mg tablet, is completely excluded from the MPP license and therefore generic versions

could remain unavailable until LPV/r patents expire in South Africa. Ultimately, governments like South Africa’s must take responsibility to ensure stock outs do not happen. Much of this relies on provincial and national government authorities establishing and implementing national minimum standards for supply chain management and resolution of stock outs on the ground. At the same time, when patent holders are the broken link in the supply chain, governments must act to overcome IP barriers and source alternative suppliers.



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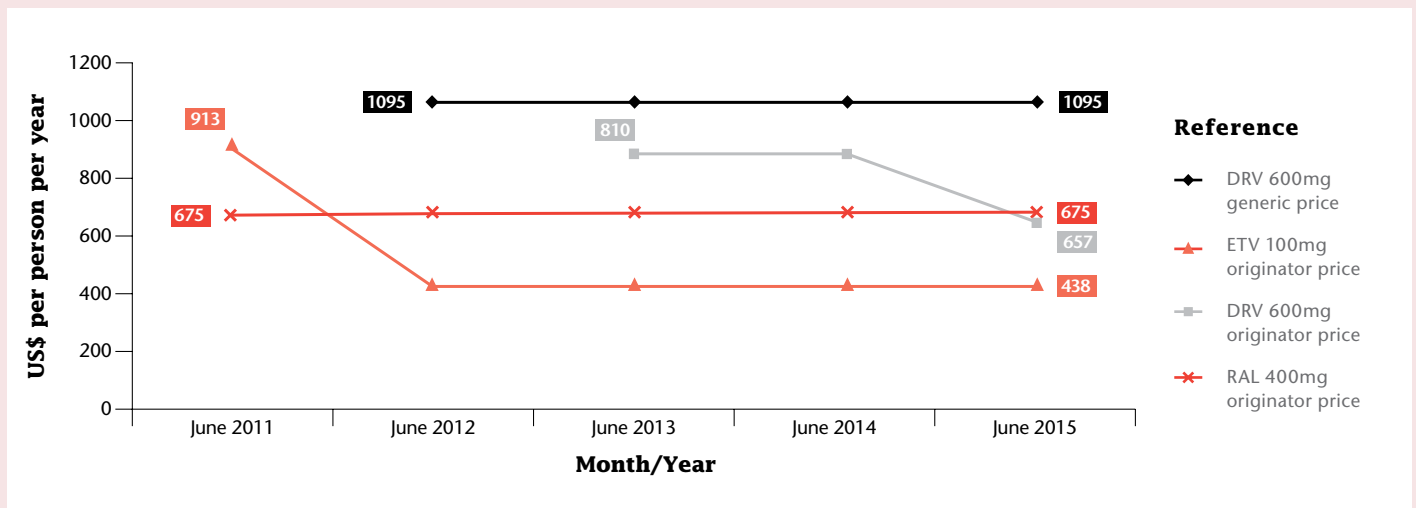
^b Stop Stockouts Project. Stockouts in South Africa, 2nd Annual Report. June 2015 [Online]. Available from: http://stockouts.org/uploads/3/3/1/1/3311088/stockouts_2014_final_online.pdf.

SPOTLIGHT ON SALVAGE TREATMENT

Prices of salvage regimens remain high. In particular, the salvage regimen of raltegravir, etravirine, darunavir and ritonavir (RAL+ETV+DRV/r) remains unaffordable. To a certain extent, this is because multiple patents on individual drugs in the regimen block the production of more affordable generic versions, and demand remains low. However, with increased access to viral load testing, more cases of treatment failure will be diagnosed, leading to increased demand for second- and third-line (salvage) regimens.

The best possible price for this combination is currently \$1,853 ppy, which has come down 33% over the last four years, but still remains hopelessly out of reach for many countries. The price of RAL has not changed since 2011, at \$675 ppy. However, the price of ETV had decreased by 52% from 2011 to 2014, from \$913 ppy to \$438 ppy, and remains the same in 2015. Meanwhile, DRV 600mg has come down by 19% since 2013, from \$810 to \$657 for the originator product version.

GRAPH 2: THE EVOLUTION IN PRICE OF SALVAGE REGIMENS



PROMISING DRUGS IN THE PIPELINE

In addition to opportunities to improve treatment regimens with existing medicines in light of new data and pricing considerations, treatments and formulations under development, or coming out of the pipeline, hold promise for further improving treatment options.

TDF to TAF

TDF is generally well tolerated as part of current first-line ART.²⁵ However, it can cause side effects relating to the kidneys and bones. A new variation with equal efficacy and fewer side effects,^{26,27} TAF, was submitted for US FDA approval in November 2014 (in combination with emtricitabine [FTC], elvitegravir [EVG] and COBI, together known as ‘the Quad’), as well as with only FTC in April 2015,²⁸ and with FTC and rilpivirine (RPV) in June 2015.²⁹

TAF is concentrated in target cells, resulting in reduced side effects. This may allow TAF to be used in younger children, but it remains unclear whether Gilead plans to test the drug in children under six years of age.

TAF also requires less API to produce than TDF, which will make TAF production less expensive.³⁰ CHAI has predicted that using TAF instead of TDF in first-line ART would decrease prices from \$51 ppy for TDF to \$19 ppy for TAF four years after the expected launch. The result would be cost savings of approximately \$345 million, if TAF is used in first-line treatments and if patents are not a barrier.¹⁹

In order to realise the full benefits of TAF, Gilead should register TAF as a single drug, which would improve availability of important future combinations with other

drugs. Gilead has registered various combinations of TAF, but has not yet registered it alone. Gilead should also expand its voluntary licence to include all MICs in the scope of the licence agreement. **[See box on page 4]**

Paediatric LPV/r

A new pellet formulation of LPV/r was finally approved by the US FDA in May 2015.³² Designed for children under three years of age, the 40mg/10mg pellets are heat stable and will replace a bad-tasting 42% alcohol suspension that requires refrigeration.³² The pellets have a similar taste to the suspension, but younger children and their caregivers still prefer them to syrup.³⁴ Additionally, a taste-masked pellet version is in the pipeline.³² Countries should expedite access to LPV/r pellets for young children by facilitating priority registration and uptake.

The CHAPAS-2 study showed that as children get older, they actually prefer paediatric tablets over pellets.³⁶ Although this may change with taste-masked formulations, it is further evidence to encourage AbbVie to expand their licence with the MPP for LPV/r, which currently only covers the suspension and pellet formulations.³⁷

❖ 3. India and trading partners: Preserve the lifesaving role of India’s existing public health safeguards, or pressure India to change IP policies for pharmaceuticals?

Thanks to public health safeguards in existing laws, India is considered to be the ‘pharmacy of the developing world’ and competition among generic manufacturers in India has resulted in substantial price reductions for ARVs. For example, 96% of the HIV medicines used by major donor-funded programmes are generics, the vast majority of which are produced in India.³⁸

However, increasingly the government of India is under pressure from pharmaceutical lobbies to modify its patent and regulatory laws and to accept IP provisions in trade

agreements that would undermine the registration and supply of affordable generics from India. There is also a range of external pressures being placed upon the Indian government by specific countries, including the US³⁹ and Japan (through the Regional Comprehensive Economic Partnership [RCEP] trade negotiations), and through upcoming trade negotiations with the European Union and the European Free Trade Association.

Amid this intense pressure, India is drafting a national IP policy, and the process has raised serious questions on whether India will retain its existing legal flexibilities and continue to employ public health safeguards in its patent system. The Ministry of Health is also considering regulatory changes that threaten to create new barriers to the development and

registration of inexpensive generic versions of medicines, including the implementation of data exclusivity and patent linkage.

Also of concern is the halting of any further use of compulsory licences, after the issuance of only one compulsory licence for a cancer drug that was priced out of reach at more than \$5,000 per month. The Indian Ministry of Health’s consideration of additional compulsory licences was met with a backlash from the same entities currently pushing for changes to India’s pharmaceutical IP policies.³⁹ India should ensure that flexibilities in its current patent and regulatory laws are retained throughout the domestic IP policy review process.

❖ 4. TPP negotiating countries: Reject provisions that impose restrictive IP protections in the TPP, or trade away access to affordable medicines?

The Trans-Pacific Partnership (TPP) is a regional trade agreement that is being negotiated between Australia, Brunei Darussalam, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the United States and Vietnam. In its current form, the agreement is the most harmful ever seen with respect to impact on access to affordable medicines in developing countries, including for ARVs and treatments for HIV co-infections. A range of proposed provisions would lengthen, strengthen and expand patent and regulatory monopolies for medicines. For example, one proposed rule limits governments' ability to restrict pharmaceutical companies' efforts to pursue 'evergreening' strategies to extend the life of pharmaceutical patents well beyond 20 years.⁴¹ Another proposed provision would create additional and unprecedented barriers to accessing clinical trial data for a new class of drugs called 'biologics'. These provisions are being pushed in particular by the US and Japan, with encouragement from pharmaceutical lobbies.⁴²

Governments should reject imposition of these new norms on pharmaceutical monopolies.

Threats to access resulting from strict IP rules exist in all countries today, regardless of level of economic development, as witnessed by the ongoing access challenges in many countries considered to be middle- and high-income and with high levels of inequality.

❖ 5. Global Fund: Introduce greater transparency and accountability in procurement policies, or risk unbalanced market influence?

The Global Fund has historically negotiated lower prices and engaged governments on how to address legal and political barriers to affordable prices. These efforts, in addition to other interventions, have been key to securing access to affordable quality-assured treatment in many countries.

However, recently, the Global Fund has changed its approach. The Market Dynamics Advisory Group (MDAG) was dissolved, and its replacements, the Strategy, Investment and Impact Committee (SIIC) and the Finance and Operational Performance Committee (FOPC), are not adequate substitutes. A recent report of the Office of the Inspector General (OIG), focusing on the Sourcing Department, found a lack of internal controls and noted "a lack of a strong internal control framework including policies, resources, tools and systems to support effective implementation of activities".⁴³

Ensuring a return to greater transparency and accountability is even more important now as the Global Fund plays an increasingly dominant role in the ARV market. The Global Fund already issues large tenders, and is now pooling its volumes and coordinating its procurement with other large purchasers, including the South African government and the United States President's Emergency Plan for AIDS Relief (PEPFAR). The Global Fund is also developing upstream relationships with API manufacturers and negotiating long-term supply agreements with drug makers. This may result in short-term benefits for the Global Fund, such as immediate cost savings, but large orders placed

by only a few major purchasers can have distorting effects on the market, impacting in particular the number of suppliers needed for a healthy market and, therefore, the cost of ARVs.

The market-shaping strategy that the Global Fund is adopting also presents concerns, including the lack of a clear position on IP, and no apparent willingness to tackle IP barriers that may emerge at the national level. Also, the potential establishment of an 'e-marketplace,' an on-line purchasing interface, may not provide full price transparency to users. This could undermine the ability of governments to negotiate affordable prices on their own or use TRIPS flexibilities when prices fail to match ability to pay and public health burden.

Other actions that could negatively impact generic competition include the promotion of tiered pricing, a commercial strategy used by multinational companies to segment markets and charge the highest price that a small percentage of the population in a particular country can pay. Additionally, the Global Fund has considered, with other organisations, establishing a task force and technical committee to address issues of drug quality, safety and efficacy. While these are important public health concerns, MSF is concerned that some partners and the prescribed approach wilfully or accidentally promote industry-centric solutions that focus on IP enforcement, rather than solutions that address the problems of quality, safety and efficacy of medicines. The current approach can result in conflation of low-cost generic medicines with counterfeit products.

MSF's analysis and recommendations on the Global Fund's market shaping strategy, procurement for impact (P4i) programme and e-marketplace are available online: <https://www.msfaccess.org/content/global-fund-market-shaping-strategy-2015>

❖ 6. Global Fund and donors: Support efforts to combat HIV, TB, and malaria in all developing countries or restrict eligibility based on income?

Over the past several years the Global Fund has suffered from underfunding. At its last replenishment conference, the Global Fund raised only \$12 billion of its \$15 billion target. In 2011, the funding shortfall was so severe that the organisation cancelled its 11th round of funding, effectively shutting the doors to new funding proposals for scale-up until 2014.

These shortfalls, and the continued flat lining of global HIV funding commitments,⁴⁴ has resulted in pressure on the Global Fund to revise the terms of eligibility for countries to receive funding, as well as the amount of 'resource envelopes' allocated for countries.

While some countries with rising incomes have been reclassified by the World Bank as 'middle-income'

countries, many are still grappling with significant burdens of HIV, TB and malaria. Currently, MSF provides HIV treatment in eight World Bank-classified MICs eligible for Global Fund funding, including: India, Kenya, Lesotho, South Africa, Swaziland, Ukraine, Uzbekistan and Yemen.

However, the Global Fund's 'New Funding Model' implemented in 2014 relied on a funding allocation formula which gave more weight to countries' 'ability to pay' based on income levels. The net result was that 55% of funds were pre-allocated to low-income countries (LICs).

As a result of shifts in the allocation distribution, several MICs such as Ukraine and Vietnam have seen their funding reduced in the 2014-2016 funding period compared to previous years, limiting their ability to reach socially excluded groups.⁴⁵ The Global Fund 'investment guidance' to Eastern Europe and Central Asia,⁴⁶ which sets limitations on ARVs and second-line TB drugs that can be

purchased by countries with Global Fund funding, is another example of how countries are restricted in their ability to utilise Global Fund support.

The Global Fund is poised to further curtail available funding for MICs, according to one proposal to be discussed in November 2015. Such limits in support for MICs are short-sighted, considering that MICs account for more than half of the global HIV disease burden⁴⁷ and simultaneously face persistent problems of equity in accessing lifesaving care. Some of these countries are also facing higher prices of drugs due to tiered pricing and patent protection.

In 2015, the Global Fund should re-integrate its commitment to helping all developing countries combat the three diseases. Donors, including BRICS countries, should ensure that the next replenishment period is well funded so that such rationing of much-needed funds between LICs and MICs does not continue.



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❖ 7. WTO TRIPS Council: Extend the LDC TRIPS waiver, or maintain a time-limited policy that risks imposing access-restricting IP rules on poor countries?

Under the WTO's TRIPS Agreement, LDCs are granted an extended 'transition period' at the end of which they must implement the terms of the TRIPS Agreement. The LDC extension is an important policy to enable access to medicines for patients in poor countries, and this transitional period (a general IP waiver that was last negotiated in 2013) currently lasts until 2021.

In February 2015, a proposal was put forward to extend the transition period for pharmaceutical IP (which was originally enacted in 2002) until countries graduate from LDC status, without prejudice to the separate, general IP waiver that remains until 2021. Extending the transition period for LDCs for pharmaceutical IP will ensure at a minimum that IP barriers are not a threat to importing affordable, generic medicines into poor countries and can provide protection against patent threats. This could encourage generic manufacturers to sell low-cost generics in LDC markets with the certainty that IP rules will not be a barrier until such countries transition from their status as LDCs.



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CONCLUSION

Strategic decisions taken in 2015 will have far-reaching effects on the future global HIV response, including the global HIV community's ability to meet the ambitious targets set by UNAIDS. The question is whether the impact will be overwhelmingly positive – or negative.

Evolving recommendations on when people with HIV should be treated, and what their treatment options will be, must make use of valuable new scientific data, or risk excluding groups from eligibility who could benefit from treatment. Decisions on IP policies in India and across the Pacific Rim region threaten to restrict access to medicines on an unprecedented scale, but a strategic, patient-centred approach could instead set important precedents on

preserving public health safeguards. Decisions by the Global Fund and WTO TRIPS Council could similarly undermine access in low- and middle-income countries – or conversely, could set important precedents to safeguard access to medicines. For their part, middle-income countries should intensify efforts to fight HIV and protect public health by championing the robust use of TRIPS flexibilities, addressing any local barriers to access affordable medicines, and contributing to global R&D.

With ART treatment access and options for many people hanging in the balance, we have a collective responsibility to ensure that the momentous opportunities in 2015 are used to advance the fight for timely, appropriate, effective and affordable treatments for all people living with HIV.

ANNEX: SUMMARY OF SECOND- AND THIRD-LINE ARV PRICES

Methods

Data for this report were collected via a questionnaire sent in May 2015 to both originator and generic companies manufacturing ARVs. The questionnaire requested information on prices for developing countries, restrictions that apply to each of the prices quoted (eligibility criteria), and any additional relevant details. The data were collected up to June 2015.

All originator companies marketing ARVs were included in the survey, but the list of generic producers is by no means exhaustive. Only generic companies that have at least one ARV quality-assured by the WHO's Prequalification Programme or US FDA at the time that the questionnaires were sent out were included in this publication.

Key considerations and limits

- ❖ The information on prices given in this publication only relates to ARVs. It does not include other costs linked to ART, such as diagnosis, monitoring or treatment of opportunistic infections.
- ❖ The manufacturers provide the prices listed in this publication. The prices paid by the purchaser may be higher due to 'add-ons' (such as import taxes and distribution mark-ups), or may be lower as a result of effective procurement procedures or as a result of negotiations. Therefore this document should not be viewed as a manufacturer's price list.
- ❖ Companies use different 'incoterms', which 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 at www.iccwbo.org.

- ❖ Originator and some generic companies have different eligibility criteria for differential pricing for countries and entities, meaning not all countries and entities can access all of the prices listed in this report.
- ❖ 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, these lists should be consulted for up-to-date information regarding quality.



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TABLE 1: PRICES OF SELECTED SECOND- AND THIRD-LINE ARV MEDICINES

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 June 2015) are in **bold**.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies			
Atazanavir (ATV)		BMS		Cipla			
		Category 1 countries	Category 2 countries	Category 1 countries	Category 2 countries		
100mg capsule	xx						
150mg capsule	2	412 (0.564)	412 (0.564)*	103 (0.142)	106 (0.146)		
200mg capsule	xx	(0.677)	(0.677)*				
300mg capsule	1			195 (0.533)	201 (0.550)		
Atazanavir/ritonavir (ATV/r)				Cipla		Emcure	Hetero
				Category 1 countries	Category 2 countries		
300mg/100mg tablet	1			243 (0.667)	243 (0.667)	243 (0.667)	237 (0.650)
Darunavir (DRV)		Janssen		Cipla	Hetero		
75mg tablet	xx	(0.113)					
150mg tablet	xx	(0.225)		(0.396)			
300mg tablet	4			1095 (0.75)			
400mg tablet	2	438 (0.600)		913 (1.25)	730 (1.000)		
600mg tablet	2	657 (0.900)		1095 (1.5)	1095 (1.500)		
Etravirine (ETV)		Janssen					
100mg tablet	4	438 (0.300)					
Lopinavir/ritonavir (LPV/r)		Abbvie		Aurobindo	Cipla	Hetero	Macleods
		Category 1 countries	Category 2 countries				
40/10mg pellets	xx				(0.16)		
80/20mg/ml oral solution	4ml	150 (0.103)	296 (0.203)		250 (0.172)		
100/25mg heat-stable tablet	3	108 (0.099)	278 (0.254)	147 (0.134)	155 (0.142)		158 (0.144)
200/50mg heat-stable tablet	4	242 (0.166)	740 (0.507)	243 (0.167)	268 (0.183)	268 (0.183)	
Raltegravir (RAL)		Merck		Hetero			
		Category 1 countries	Category 2 countries				
400mg tablet	2	675 (0.925)	Case-by- case basis	1752 (2.400)			
100mg tablet		(0.60)	Case-by- case basis				
25mg tablet		(0.30)	Case-by- case basis				

* Atazanavir 150mg caps 60's @ ZAR 229.04; and 200mg caps 60's @ ZAR 274.85. BMS bills South Africa in Rand (ZAR) to avoid fluctuation due to exchange rate.

Viiv offers at-cost price for DTG (depending on volume) in least-developed countries, sub-Saharan Africa and low-income countries as part of a Medicines Patent Pool agreement for public market tenders until a generic product is approved. In middle-income countries, price varies based on Gross Domestic Product and impact of HIV epidemic in the country.



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GLOSSARY AND ABBREVIATIONS

API: Active pharmaceutical ingredient.

ART: Antiretroviral therapy to treat HIV/AIDS.

ARV: Antiretroviral medicine to treat HIV/AIDS.

ATV: Atazanavir, protease inhibitor.

ATV/r: Atazanavir/ritonavir; boosted protease 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.

CHAI: Clinton Health Access Initiative. Since 2002, the Clinton Health Access Initiative has assisted countries in implementing large-scale, integrated care, treatment and prevention programs.

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.

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; integrase inhibitor.

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

ETV: Etravirine; non-nucleoside reverse transcriptase inhibitor.

EVG: Elvitegravir; integrase 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.

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

IP: Intellectual property.

LDC: Least-developed country; according to United Nations classification.

LIC: Low-income country; according to World Bank classification.

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

MIC: Middle-income country; according to World Bank classification.

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.

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 linkage: Links regulatory approval of a generic medicine to patent status, prohibiting national drug regulatory authorities from approving generic medicines until patents have expired.

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

PPY: Per person 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.

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

RAL: Raltegravir; integrase inhibitor.

RCEP: Regional Comprehensive Economic Partnership, a trade agreement currently under negotiation between the member states of ASEAN, plus Australia, China, India, Japan, New Zealand and South Korea.

RPV (or RIL): Rilpivirine, non-nucleoside reverse transcriptase inhibitor.

RTV: Ritonavir; protease inhibitor.

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 Darussalam, Chile, Canada, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the US and Vietnam.

TRIPS: Trade-related Aspects of Intellectual Property Rights.

UNITAID: Is an international drug purchase facility that was established in 2006 by Brazil, Chile, France, Norway and the United Kingdom, and now includes 27 countries to provide new sources of funding to fight HIV/AIDS, malaria and tuberculosis.

US FDA: United States Food and Drug Administration.

ViiV Healthcare: Joint venture created in 2010 by GlaxoSmithKline, Pfizer and Shionogi focusing on the research, development 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.

WHO: World Health Organization.

WTO: World Trade Organization.

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