



medicines
patent
pool



PROGRESS AND ACHIEVEMENTS
OF THE MEDICINES PATENT POOL
2010 - 2015

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Founded by UNITAID in July 2010, the Medicines Patent Pool (MPP) is an innovative mechanism offering a public health-driven business model that aims to lower the prices of HIV medicines and facilitate the development of better-adapted HIV treatment through voluntary licensing and patent pooling.

Five years later, the organisation has made significant progress, signing voluntary licences on **12 priority antiretrovirals** (ARVs) with six patent holders and 59 sub-licences with 14 generic manufacturers. Its generic partners have supplied more than six million patient-years of WHO-recommended ARVs in **117 countries**, including 41 countries that were previously unable to benefit from generic competition for such medicines.

The organisation's licences have saved the international community **USD 79 million through lower prices of ARVs**, equivalent to **one-year of treatment for 625,000 people**. In the coming years, it is expected to generate total savings of between **USD 1.18 and 1.4 billion**. **New fixed-dose combinations and paediatric formulations** that will enable more people living with HIV to access improved formulations with better safety and efficacy profiles or more convenient dosing schedules are also under development.

The MPP's main achievements to date are highlighted below.

NEGOTIATING LICENCES TO INCREASE ACCESS IN DEVELOPING COUNTRIES

The first step for the MPP is to identify the priority ARVs for which licences are needed.¹ The organisation then seeks to enter into licensing negotiations with the patent holders. Licences aim to: (i) enable manufacturing or sale of ARVs in countries in which they are patented; (ii) enable more countries to benefit from access to more affordable generics; and (iii) include public-health friendly terms and conditions to enhance competition and promote innovation and access. To date, the MPP has negotiated licensing agreements for 12 ARVs. Table 1 provides an overview of the MPP licences.

¹ See latest edition of the *Antiretroviral Priorities of the Medicines Patent Pool*, available at www.medicinespatentpool.org/target-medicines

Table 1 – ARVs licensed to the MPP

| ARV | PATENT HOLDER | PLACE IN TREATMENT (WHO) | DATE OF LICENCE |
|-------------------------------------|----------------------------------|--------------------------|-----------------|
| Abacavir (ABC) (paediatric) | ViiV Healthcare | first-line paediatric | February 2013 |
| Atazanavir (ATV) | Bristol-Myers Squibb | second-line adult | December 2013 |
| Cobicistat (COBI) | Gilead Sciences | new ARV | July 2011 |
| Darunavir (DRV) ² | US National Institutes of Health | third-line | September 2010 |
| Dolutegravir (DTG) | ViiV Healthcare | new ARV | April 2014 |
| Elvitegravir (EVG) | Gilead Sciences | new ARV | July 2011 |
| Emtricitabine (FTC) | Gilead Sciences | first and second-line | July 2011 |
| Lopinavir (LPV) (paediatric) | AbbVie | first-line paediatric | December 2014 |
| Raltegravir (RAL) (paediatric) | MSD (Merck in the US and Canada) | third-line paediatric | February 2015 |
| Ritonavir (RTV) (paediatric) | AbbVie | first-line paediatric | December 2014 |
| Tenofovir alafenamide (TAF) | Gilead Sciences | new ARV | July 2014 |
| Tenofovir disoproxil fumarate (TDF) | Gilead Sciences | first-line adult | July 2014 |

Why Licences on ARVs?

The need for licensing in the field of ARVs stems from a significant surge in patenting of ARVs in developing countries.³ This increase is particularly pronounced in key countries of manufacture of generic medicines such as India⁴ and China from which many developing countries import their ARVs. Patents in such countries, and in some cases patent applications, can impact the ability of importing countries to purchase generic ARVs, unless there are licences in place that make it possible.

Early voluntary licences in HIV generally benefitted few countries, were issued to a handful of suppliers, sometimes only one, were known to contain many restrictions, and detailed terms and conditions were not publicly available. With the entry of the MPP, the trend towards more widespread licensing of ARVs by patent holders has accelerated, with broader geographical coverage, greater competition and improved terms and conditions, enabling more robust competition.⁵

² In September 2010, the MPP obtained a licence on darunavir-related patents from the US National Institutes of Health. At the time, however, there were other patents on DRV held by other patent holders.

³ Moon S. et al, 'ARV patents on the rise? An analysis of ARV patent status in 75 low- and middle-income countries' presented at International AIDS Conference, 25 July 2012, www.medicinespatentpool.org/wp-content/uploads/ARV-Patenting-Trends-FINAL2.pdf.

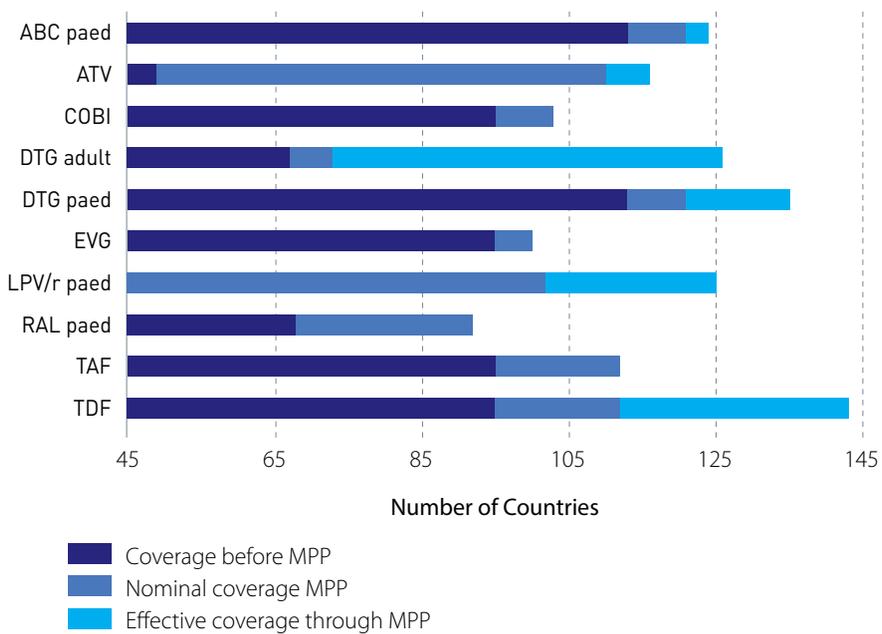
⁴ Early ARVs were not patented in India. Among the more recent ARVs, at least six have compound patents granted in India and a further three have pending patents. Several other so-called "secondary patents" are either pending or granted that may impact competitive manufacturing or supply of ARVs in India and importing countries.

⁵ WHO/WIPO/WTO, *Promoting Access to Medical Technologies and Innovation*, 2013; *Access to Medicines Index*, November 2014.

EXPANDING THE GEOGRAPHICAL SCOPE OF VOLUNTARY LICENCES

One of the most important features of voluntary licences is the geographical scope, i.e. the number of countries that will be able to benefit. MPP licences enable the manufacturing of generic adult formulations of ARVs and their sale in countries where between **87 and 93% of people with HIV in the developing world** live.⁶ This includes all 34 low-income countries and, depending on the licence, between **55% and 80% of middle-income countries**, representing a significant increase over licences prior to the establishment of the MPP. Figure 1 provides an overview.

Figure 1 – Geographical Scope Expansion in MPP Licences



In Figure 1, “nominal coverage” includes countries explicitly covered in the MPP agreements. “Effective coverage” includes any additional countries able to purchase generics as a result of certain unique flexibilities negotiated in the framework of the agreement. Further information on this is provided in the text boxes on dolutegravir and tenofovir disoproxil fumarate.⁷

⁶ These figures relate to licences on adult formulations. For paediatric formulations, licences cover countries that are home to 98-99% of children living with HIV worldwide.

⁷ Note that licences also allow manufacturers to supply other countries that issue compulsory licences. This, however, is not included in the calculations.

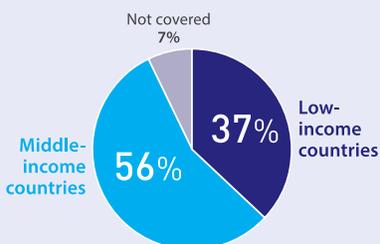
Geographical Expansion for Dolutegravir

Dolutegravir (DTG) is a very promising new ARV that received FDA regulatory approval in 2013 and was licensed to the MPP in April 2014 by ViiV Healthcare.⁸ The pre-existing licensing policy of the patent holder covered 67 low- and middle-income countries accounting for 80% of people living with HIV. The geographical expansion of the MPP licence has two components. First, six additional middle-income countries were included in the licence, which collectively account for 9.3% of people living with HIV in the developing world (Egypt, India, Indonesia, the Philippines, Turkmenistan and Vietnam). For these countries a differentiated royalty scale was agreed according to the country income level (5% to 10%) that will enable treatment programmes to purchase more affordable generics.

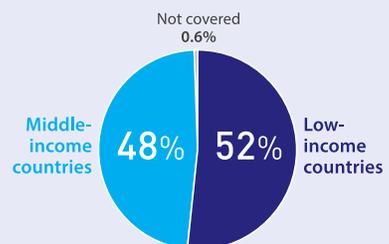
Second, the licence allows sale of generic DTG in all countries outside the licensed countries in which DTG is not patented even if the ARV is patented in the country of manufacture, such as China, India or South Africa.⁹ Thanks to this provision in the licence, many additional countries will be able to procure generic dolutegravir from MPP licensees. **In total, 127 countries – including 92 middle-income countries – that are home to 93.4% of people living with HIV in LMICs will be able to benefit from the voluntary licence on DTG.** Given the likely importance of DTG in future HIV treatment, the geographic expansion achieved by the MPP licence will have significant implications for many countries once generic manufacturers reach the market (expected in 2016/17).

The MPP paediatric licence on DTG includes 121 countries and also enables sale into additional countries in which there are no patents. Thus, the paediatric licence covers countries home to 99.3% of children living with HIV.

DTG Adult Licence Effective Coverage in LMICs (by PLHIV)



DTG Paediatric Licence Effective Coverage in LMICs (by CLHIV)



⁸ Burrone E. and Perry G., 'Affordability of New HIV Treatments', *The Lancet*, Vol. 384, p. 853, 6 September 2014.

⁹ Note that the product is patented in China and South Africa and the patent is pending in India. Under the licence, manufacturing can happen anywhere in the world.

The Case of Tenofovir Disoproxil Fumarate (TDF)

MPP's licence with Gilead Sciences provides another example of the benefits of MPP-negotiated terms in encouraging robust generic competition and lower prices for an important ARV in many more countries. The patent holder's pre-existing policy allowed its generic licensees to sell in 95 countries. The MPP licence expanded the number of countries in two ways. First, the licence allowed sale in 17 additional countries (reaching 112). In addition, in light of the limited patenting of TDF in developing countries, the agreement included a specific flexibility that enabled generic manufacturers to supply many more middle-income countries that they could not supply previously.¹⁰ This provision enabled several countries to benefit from generic competition and procure this key first-line drug at lower prices. Today, there is robust generic competition for generic TDF first-line formulations in the vast majority of developing countries. Further information is provided in the chapter "Savings Generated to Date".

NEGOTIATING IMPROVED TERMS AND CONDITIONS

In addition to broad geographical scope, several other licensing terms and conditions are important for access as they determine what licensees can and cannot do. The **MPP negotiates licences from a public health perspective**, which has resulted in demonstrably better terms and conditions¹¹, compatibility with the use of TRIPS flexibilities, maximum flexibility for the licensees,¹² and unprecedented transparency in licensing. Table 2 provides an overview of licensing terms and conditions before and with the MPP.

¹⁰ This was achieved through an "unbundling" provision, which enabled generic manufacturers to take the licences on all Gilead ARVs and subsequently terminate the tenofovir part (a flexibility that was introduced by the MPP).

¹¹ *Access to Medicines Index*, November 2014.

¹² See, for example, UK All-Party Parliamentary Group on AIDS, *Access Denied*, December 2014.

Table 2 – Licensing terms and conditions

| LICENSING TERMS | PRIOR TO MPP | MPP LICENCES |
|--|---|--|
| Publication of agreements | Licences were not published | All MPP licences have been made public in full |
| Number and selection of licensees | Lack of clarity on licensee selection; some licences with limited number of manufacturers, or only one API manufacturer, resulting in limited price competition; others with limited follow-up to ensure prompt development | Number and quality of licensees carefully vetted through non-exclusive and non-discriminatory process; licensee performance closely monitored to ensure prompt development, and registration |
| Possibility to sell outside licensed countries under certain circumstances | While detailed provisions are unknown due to confidentiality of licences, many instances have been recorded in which it has not been allowed ¹³ | Addressed in different licences in different ways: all MPP licences allow sale to countries issuing compulsory licences; some include broad provisions allowing sale to countries where there is no patent infringement; others provide licensees the option to terminate in the event that underlying patent situation changes, enabling supply to more countries |
| Possibility to combine products into appropriate FDCs or develop adapted paediatric formulations | Details unknown due to confidentiality of licences, but restrictions are known to have been present in some licences | Covered in all licences |
| Freedom to supply countries issuing compulsory licences | Unlikely present in previous agreements, but details unknown due to confidentiality of licences | Available in all MPP licences |
| Freedom to challenge patents | Details unknown due to confidentiality of licences, but no-challenge clauses known to be present in some licences | Full flexibility for licensees to challenge licensed patents in all MPP licences |
| Quality assurance | Unknown | All licensees require approval from the WHO Prequalification Program or from a Stringent Regulatory Authority |
| Data exclusivity waivers | Unknown due to confidentiality of licences | Included in all MPP agreements |
| Purchase of active pharmaceutical ingredient (API) | Detailed provisions unknown, but cases known in which API could only be purchased from licensor | In all MPP licences, licensees can manufacture their own API, sell API to others, or purchase API from other manufacturers |
| Patent disclosures | List of patents owned by patent holders generally not disclosed and in many cases difficult to retrieve elsewhere | List of patents and their status disclosed in licences including, in some cases, patents in countries outside the licensed territory |

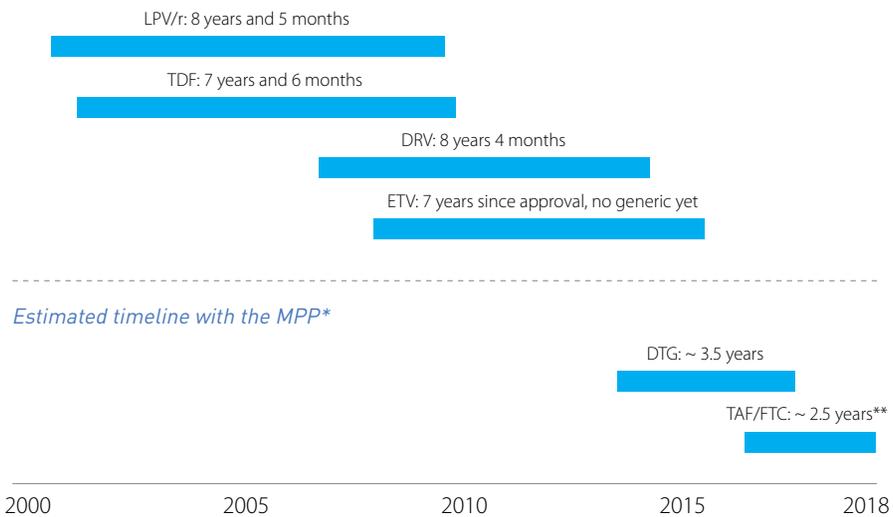
¹³ See, for example, instances related to second-line treatment cited in WHO, *Increasing Access to HIV treatment in Middle-income Countries*, 2014.

ACCELERATING GENERIC MARKET ENTRY

The MPP was established to accelerate the availability of quality assured generics. Historically, it has taken five to ten years for a new ARV to become available as a quality assured (QA) generic for use in developing countries, and even more time was required to have at least two QA suppliers.¹⁴ Patents or patent applications on many of the new ARVs in key countries of manufacture (such as India) could delay this timeline even further. MPP licences will allow generics to reach developing countries with quality assured treatments faster.

Figure 2 – Timelines from originator approval to availability of at least two quality assured generics.

Historical timeline



- * Estimates based on current information. May change depending on complexity of molecule, WHO guidance, market forecasts and time taken for regulatory review.
- ** This may vary depending on whether, when and in which formulations TAF is approved by regulatory authority

MPP is shortening this timeline by negotiating licences as early as possible, in some cases even before they receive regulatory approval, which enables generic manufacturers to begin development earlier. The preparation of joint forecasts with the World Health Organization, technical support to licensees where appropriate and licence management with regular reviews of development plans also help to facilitate and accelerate the development process.

¹⁴ Defined as those approved by the WHO Prequalification or by a Stringent Regulatory Authority such as the US FDA or the European Medicines Agency.

COORDINATING THE DEVELOPMENT OF NEEDED PAEDIATRIC FORMULATIONS

In addition to improving access to quality assured generics of new ARVs, the MPP is also playing a central role in **accelerating the development of much needed paediatric formulations.**

The WHO meetings on Paediatric ARV Drug Optimization (PADO 1 and 2) identified the priority formulations needed to implement the new treatment guidelines, as well as other formulations that would be key to improve paediatric treatment outcomes in the future. In order to address the many challenges associated with their development and delivery, the MPP, in cooperation with UNITAID, the Drug for Neglected Diseases *initiative* (DND*i*) and the Clinton Health Access Initiative (CHA), established the Paediatric HIV Treatment Initiative (PHTI) in 2014. The PHTI, together with its technical partner the WHO, is working through product-specific working groups and expects to deliver three needed paediatric formulations by 2017.¹⁵

Table 3 – Projects under the Paediatric HIV Treatment Initiative

| FORMULATION | STATUS |
|----------------------|---|
| ABC/3TC/EFV | Licences obtained (ABC/3TC) Working group established Studies on weight band dosing schedule completed Generics invited to participate in development through an open expression of interest process Filing for approval expected in 2016 |
| DRV/r | Non-assert policy on DRV expanded Licence on certain formulations of ritonavir obtained Working group established Studies on weight band dosing schedule under way Filing expected in 2017 |
| Raltegravir | Licence obtained Modeling on weight band dosing schedule under way |
| LPV/r | Licence obtained Under development by generic partners |
| ABC(or)AZT/3TC/LPV/r | Licences obtained (ABC/3TC and LPV/r) Under development by DND <i>i</i> and generic partners |
| ATV/r | Licences obtained |
| DTG | Licence obtained |
| DTG/XTC/TAF | Licences obtained (DTG and TAF) |

In order to facilitate the re-formulation and supply the new combinations in developing countries, the MPP has negotiated licences with most of the pharmaceutical companies that have patents on the priority ARVs, significantly expanding the number of countries that generic manufacturers of paediatric formulations will be able to supply. All MPP paediatric licences enable sale in countries where at least **98% of children with HIV live**. Some include specific provisions to enable availability of new formulations in high-income countries as well, so that all children living with HIV can have access.

¹⁵ On December 1 2014, PEPFAR and the Global Fund joined hands with the PHTI on a Commitment-to-Action to contribute to addressing some of the other challenges in relation to the development and uptake of new paediatric formulations.

WORKING WITH GENERIC MANUFACTURERS TO DELIVER NEEDED MEDICINES

Fourteen generic manufacturers have signed licences with the MPP enabling them to deliver needed medicines in additional countries. This includes many of the leading suppliers of APIs or finished formulations to the developing world. The full list of licensees per ARV is available in Annex II.

In order to enhance robust generic competition, the MPP has worked on **expanding the manufacturing base for ARVs**. One specific example is Desano, the first Chinese company ever to receive a voluntary licence on an ARV, now joined by HEC Group and Huahai. Since many of the new ARVs are patented in China, Chinese companies have been unable to supply API or finished formulations of many ARVs for use in developing countries.¹⁶ Chinese generic companies have demonstrated cost efficiencies in manufacturing APIs, but patents have restricted production of certain ARVs. This is likely to change with Chinese manufacturers taking licences from the MPP and being able to contribute to further price reductions for important ARVs such as TDF.

The following formulations are currently on the market as quality assured formulations from MPP generic licensing partners:

- Abacavir oral solution 20mg/ml
- Abacavir 60mg + lamivudine 30mg tablets
- Atazanavir capsule 100, 150, 200, 300mg
- Atazanavir/ritonavir tablet 300/100mg
- Tenofovir disoproxil fumarate tablet 300mg
- Tenofovir disoproxil fumarate/emtricitabine tablet 300/200mg
- Tenofovir disoproxil fumarate/emtricitabine/efavirenz 300/200/600mg
- Tenofovir disoproxil fumarate/lamivudine 300/300mg
- Tenofovir disoproxil fumarate/lamivudine/efavirenz 300/300/600mg

DEVELOPING THE FUTURE OF HIV TREATMENT

The MPP is also working with its partners on delivering new HIV treatment regimens. ARVs with **improved efficacy, lower side effects, lower dose or potential for lower price**, such as dolutegravir and possibly TAF, are likely to be central to future HIV treatment. MPP generic partners are already developing these ARVs and will formulate them in appropriate combinations in line with recommendations from the WHO. An overview table of current and possible future ARVs resulting from MPP licences is provided in Annex II.

¹⁶ For patented ARVs, manufacturing in China has generally been limited to intermediates used for the manufacturing of the active pharmaceutical ingredient (API).

SAVINGS GENERATED TO DATE

Through its licences, the MPP aims to generate savings to the international community by reducing prices of ARVs through robust generic competition. The first MPP licence on TDF has already generated **USD 78 million** in savings (as of end 2014), equivalent to one year's treatment for approximately **625,000 people**.¹⁷

Lower royalties for TDF and TDF-combinations, as well as the ability of generic manufacturers to sell in more countries, have allowed governments and international agencies to buy the drugs at lower prices.¹⁸ TDF-formulations were supplied to 115 countries including 20 countries outside of the pre-existing 95-country policy of the originator company. Further details on the methodology for estimating savings are provided in Annex II.

Figure 3 – Savings generated by MPP (2012-2014) in USD mn

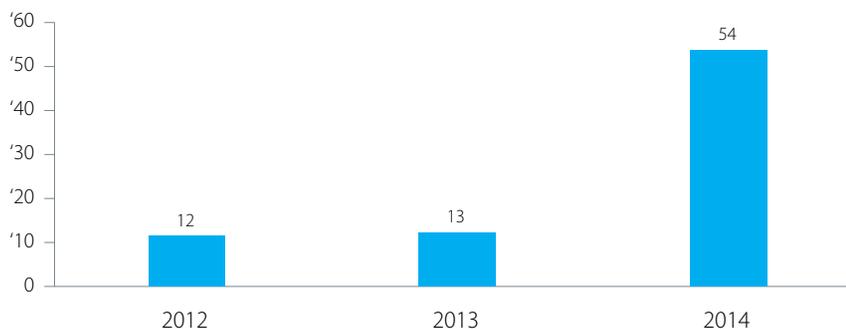


Table 4 provides an illustrative list of countries that have been able to benefit from enhanced generic competition and, as a result, purchase TDF or TDF-based combinations at a lower price. The figures are based on information available in WHO's *Global Price Reporting Mechanism (GPRM)*.

¹⁷ Assuming a price of USD 126 per patient per year as per prices quoted for 2014 in the WHO *Global Price Reporting Mechanism (GPRM)* for TDF/3TC/EFV.

¹⁸ For example, Esgueira P. R., 'Patent related issues during ARV Procurement processes – country experiences', IDA Foundation, June 2012, presented at the International AIDS Conference in Washington 2012 and at the WHO AMDS meeting. WHO, *Increasing access to HIV treatment in middle-income countries*, May 2014. Also, letters submitted to UNITAID by UNICEF, PSCMS and IDA Foundation in 2014.

Table 4 - Prices for TDF and TDF-combinations following MPP agreement in an illustrative list of countries. Prices displayed in US dollars per patient per year.

| COUNTRY | PRODUCT | LOWEST PRICE PAID BEFORE MPP AGREEMENT (2010-2011) | LOWEST PRICE FROM MPP PARTNERS FOLLOWING MPP AGREEMENT (2011-12) | LOWEST PRICE FROM MPP PARTNERS (2013-14) |
|-------------|---------|--|--|--|
| Azerbaijan | TDF/FTC | 582 | 80 | - |
| Belarus | TDF/FTC | 577 | 77 | 67 |
| Egypt | TDF/FTC | 384 | 85 | 76 |
| El Salvador | TDF/FTC | 553 | 72 | 61 |
| Georgia | TDF/FTC | 657 | 88 | - |
| Iran | TDF | 577 | 48 | 48 |
| Iraq | TDF | 440 | 55 | 55 |
| Paraguay | TDF/FTC | 536* | - | 86 |
| Tunisia | TDF/FTC | 358 | 118 | 95 |

TDF: Tenofovir disoproxil fumarate; TDF/FTC: tenofovir disoproxil fumarate /emtricitabine
 * 2012 price

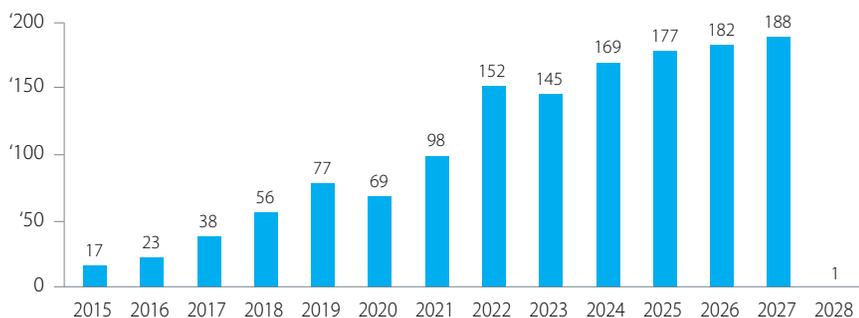
Source: Analysis based on data from the WHO *Global Price Reporting Mechanism*

Savings from other MPP licences are expected to gain momentum in the coming months as generic manufacturers work on the development and registration of ARVs and are able to begin supply. For products that already exist as quality assured generics from at least one supplier, the timeline from an MPP agreement to measurable savings is approximately one year. For new ARVs, savings are likely to start three-four years after the MPP licence is signed.

PROJECTED SAVINGS INTO THE FUTURE

Total projected economic savings to be generated by the MPP **are estimated to be between USD 1.18 billion and USD 1.4 billion by 2028**, a total of at least 20 dollars in savings for every dollar invested in the MPP. This takes into account savings from MPP licences from its inception until 2028, the date of expiry of the last patent on medicines that are currently identified as priorities for the MPP. Eighty-seven percent of these savings are expected to occur in relation to ARVs that have already been licensed to the MPP, whereas the remaining 13% will depend on whether the MPP succeeds in obtaining licences on additional ARVs in the future.

Figure 4 – Projected Savings from MPP Licences (2015-2028) in USD mn



The savings generated by the MPP are defined as the funds that purchasers (i.e. governments, donors, others) would not have to pay to treat the same total number of people. The figure only pertains to the estimated increase in the number of people having access to cheaper treatment as a result of the MPP's work in low- and middle-income countries. It therefore only accounts for forecasted sales in additional countries that are newly able to benefit from the purchase of ARVs over and above those that were in pre-existing licences or that were already benefitting from generic competition. The baseline scenario is assumed to be a continuation of preceding originator licensing and pricing practices for all their products. It includes a series of conservative assumptions, some of which are explained in Annex III.

The model is based on forecasts developed in partnership with the World Health Organization. It is updated regularly to account for changing circumstances, new data and new medicines advancing through the pipeline.

ENHANCING TRANSPARENCY THROUGH THE MPP PATENT STATUS DATABASE

Prior to the publication of the MPP Patent Status Database, information on the patent status of ARVs was publicly available for approximately 40 developing countries.¹⁹ Moreover, this information was not available in a single location, often difficult to retrieve, not updated on a regular basis and limited to a few ARVs. The launch of the MPP Patent Status Database in April 2012 has resulted in unprecedented transparency on what ARVs are patented where. Over the years, it has become a key reference for most international ARV agencies such as UNICEF, the Partnership for Supply Chain Management (PFSCM) or the IDA Foundation procuring ARVs on behalf of national treatment programmes, as well as many other organisations and individuals working in the HIV and access to medicines field.

To date, the MPP Patent Status Database contains information on **24 ARVs in 89 countries**. The database is regularly updated and a new structure will be launched in late 2015 or early 2016 to include a number of additional features and make it easier to download information for further analysis.

¹⁹ UNITAID, *Patent Pool Initiative Implementation Plan, November 2009*.

ANNEX I – ARVS PER LICENSEE*

| AUROBINDO | CIPLA | DESANO | EMCURE | HEC GROUP |
|--|--|---|--|---|
| Abacavir (paed) Atazanavir Cobicistat Elvitegravir Emtricitabine TAF | Atazanavir Cobicistat Dolutegravir Elvitegravir Emtricitabine TAF | Atazanavir Cobicistat Dolutegravir Emtricitabine TAF TDF | Atazanavir Cobicistat Dolutegravir Elvitegravir Emtricitabine TAF | Cobicistat Emtricitabine TAF TDF |
| HETERO | HUAHAI | LAURUS | LUPIN | MICRO LABS |
| Cobicistat Dolutegravir Elvitegravir Emtricitabine Lopinavir (paed) Ritonavir (paed) TAF | Cobicistat Emtricitabine TAF TDF | Cobicistat Dolutegravir Elvitegravir Emtricitabine TAF TDF | Dolutegravir | Dolutegravir |
| MYLAN | SHASUN | SHILPA | STRIDES | |
| Dolutegravir | Cobicistat Elvitegravir Emtricitabine TDF | Cobicistat Elvitegravir Emtricitabine TDF | Dolutegravir | |

* Aurobindo, Cipla, Emcure and Hetero also took the TDF licence and made use of the “unbundling” provision, therefore being able to supply TDF to additional countries (as explained above).

ANNEX II - OVERVIEW OF ONGOING DEVELOPMENTS BASED ON ARVS ALREADY LICENSED TO THE MPP **

| ARV | Active pharmaceutical ingredients currently under development by MPP Licensees | Adult formulations currently being developed or scheduled for development by MPP Licensees | Possible New Adult Formulations For Development by MPP Licensees ** | Paediatric formulations currently being developed or scheduled for development by MPP licensees | Possible New Paediatric Formulations For Development by MPP licensees ** |
|-------------------------------------|--|--|---|---|--|
| Abacavir | Already developed | | ABC/3TC/DTG # | ABC/3TC/EFV dispersible # % LPV/r-ABC/3TC/ sprinkles # % | |
| Atazanavir | Already developed. More under development. | ATV 300mg* ATV/r 300/100mg* | ATV/c # | ATV 150mg* ATV 200mg* | ATV/r # % ATV/c powder for oral use # |
| Cobicistat | Under development # | TDF/FTC/EVG/COBI (Quad) # | ATV/c # DRV/c # | | ATV/c # DRV/c # |
| Darunavir | Already developed | | DRV/c # | DRV/r # % | |
| Dolutegravir | Under development # | DTG 50mg # | TDF/3TC/DTG # TDF/FTC/DTG # TAF/3TC/DTG # TAF/FTC/DTG # ABC/3TC/DTG # | | DTG 25mg granules # DTG 10mg granules # DTG dispersible tablets # ABC/3TC/DTG # |
| Elvitegravir | Under development # | TDF/FTC/EVG/COBI (Quad) # | EVG/c # | | |
| Lopinavir | Already developed | | | LPV/r sprinkles # LPV/rABC/3TC # % LPV/rAZT/3TC # % | |
| Raltegravir | Already developed | | | RAL dispersible tabs # | |
| Ritonavir | Already developed | ATV/r 300/100mg* | | DRV/r # % LPV/r sprinkles # LPV/rABC/3TC # % LPV/rAZT/3TC # % | ATV/r # |
| Tenofovir alafenamide [^] | Under development # | TAF/FTC # | TAF/3TC# TAF/3TC (or FTC)/EFV # TAF/3TC (or FTC)/EFV(400mg) # TAF/3TC (or FTC)/DTG # | | TAF/3TC (or FTC)/EFV # TAF/3TC (or FTC)/DTG # |
| Tenofovir disoproxil fumarate (TDF) | Already developed. More under development | TDF/3TC (or FTC)/EFV* TDF/FTC/EVG/COBI (Quad) # | TDF/3TC (or FTC)/EFV(400mg) # TDF/3TC (or FTC)/DTG # | | TDF/3TC (or FTC)/EFV # TDF/FTC/EFV # TDF/3TC/DTG # |

* ARVs for which at least one quality assured generic manufacturers already on the market. MPP's work focuses on increasing number of manufacturers to enhance competition and enable sale in additional countries through improved terms and conditions.

ARVs for which no quality assured generic manufacturer currently available. MPP working with its licensees to develop QA sources (API and finished formulations).

[^] Originator TAF has not yet received regulatory approval. Generics are already working on the development of the API. Specific formulations will follow once/if product is approved and there is greater clarity on needed formulations.

** Illustrative lists subject to changes based on WHO treatment guidelines, market forecasts and recommendations for treatment optimization made by experts in the context of WHO's work on treatment optimisation (e.g. CADO and PADO Conferences)

% PHTI Project

ANNEX III – SUMMARY OF METHODOLOGY FOR CALCULATING SAVINGS

The methodology for calculating savings from MPP's first licence for tenofovir disoproxil fumarate includes two components. First are the savings linked to a reduction in royalties that generic manufacturers pay to originator companies. Prior to the MPP licence, generic manufacturers with a licence on TDF were paying 5% royalties to the patent holder. Following the MPP licence, licensees were able to either no longer pay any royalties or pay lower royalties (3%). In both cases, this has enabled generic manufacturers to quote lower prices in TDF tenders and generated savings to countries from the purchase of TDF and TDF-based combinations.

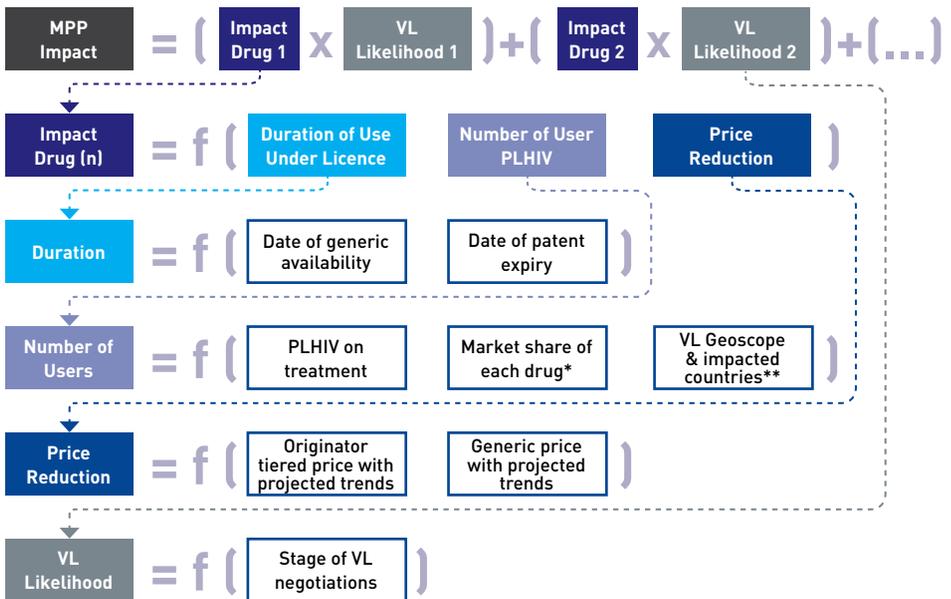
A second source of savings has resulted from generic manufacturers selling TDF and TDF-based formulations to countries outside the 95 countries that were a part of the pre-existing licensing policy of the originator company. This includes, for example, the countries that are listed in table 4 on page 11, as well as several others. The calculations are based on the difference between the weighted average price at which such countries were buying TDF prior to the MPP licence (calculated from the WHO's *Global Price Reporting Mechanism* (GPRM)), often from the originator company, and the price at which they have been able to procure it subsequently from the MPP generic partners thanks to enhanced generic competition. Volumes and price of current sales are based on data reported by the manufacturers themselves.

The methodology is based on the assumption that all countries outside the 95-country territory were buying at prices equivalent to the weighted average price of countries listed in the GPRM. Taking into consideration that the GPRM only includes sales in donor-funded countries, which are generally able to benefit from lower prices than other countries, this may result in an underestimation of the actual price difference in other countries and hence an underestimate of savings. The calculations also focus exclusively on finished formulations and do not include sales of API by MPP generic partners, which may have also resulted in additional savings.

ANNEX IV – METHODOLOGICAL OVERVIEW FOR CALCULATING PROJECTED SAVINGS

The following chart provides a visual overview of the methodology used by the MPP in estimating projected savings.

Determinants of MPP’s Economic Impact and Methodology



* Basis forecasts developed in consultation with WHO

** Only additional countries in MPP licences considered (over & above existing licensing policies)

The model is based on the following main variables:

- For each ARV, impact duration starts on the estimated date of conclusion of the licence and ends one year after the expiry of the main blocking patent (secondary patents are generally not considered with few exceptions);
- For pipeline ARVs, the impact start date is two years after the ARV’s market authorisation. Impact for each ARV ends at the time of expiry of the relevant patent and overall impact ends in 2028 at the expiry of the last patent on a current priority medicine.
- The model reviews net additional number of people having access to a particular generic ARV due to MPP’s work (treatments for people in countries covered by pre-existing VLs are not counted). The calculations are based on projected market adoption of each ARV as per the market forecast developed by the MPP, in collaboration with the WHO.

- The prices reflect the difference between the ARV's baseline price and its reduced price due to the MPP's intervention. The baseline price is based on the weighted average of the originator tiered pricing by country derived from Médecins Sans Frontières' *Untangling the Web* (UTW) and WHO's *Global Price Reporting Mechanism*.
- The ARV's impact price is based on an international industry historic average of year-over-year erosion rates of originator prices due to introduction of generic competition.
- For ARVs for which licences have not been completed, the impact on that ARV has been multiplied by a probability factor (VL Likelihood), which takes into account the probability of getting a licence on those ARVs based on the current engagement with the patent holder.

The model currently only includes medicines that are already approved or at least in Phase III development. Impact with Phase II products would be higher.

Many of the assumptions included in the model are conservative and likely underestimate actual impact. It is important to note, for example, that the projected savings do not include: (i) possible future savings from licensing compounds that are currently in early stage clinical trials (i.e. Phases I and II); (ii) efficiencies in procurement generated by the transparency created by the MPP Patent Status Database; (iii) savings from licences covering secondary patents (with few exceptions); (iv) savings from additional competition generated by MPP licences in countries already covered by pre-existing licences; (v) effects of the normative changes created by the MPP through spread of licensing terms negotiated by the MPP in its licences.

In addition, the model focuses only on direct economic impact. However, there is likely to be significant public health impact from the development of needed paediatric formulations, earlier availability of fixed-dose combinations on new ARVs based on MPP licences; and earlier availability of products with improved efficacy and/or lower side effect profile.

ACRONYMS

| | |
|---------------|--|
| AIDS | acquired immune deficiency syndrome |
| API | active pharmaceutical ingredient |
| ARV(s) | antiretroviral(s) |
| FDA | United States Food and Drug Administration |
| FDC(s) | fixed-dose combination(s) |
| GPRM | <i>Global Price Reporting Mechanism</i> |
| HIV | Human Immunodeficiency Virus |
| IP | intellectual property |
| LMICs | low- and middle-income countries |
| MPP | Medicines Patent Pool |
| PADO | Paediatric ARV Drug Optimization |
| PFSCM | Partnership for Supply Chain Management |
| QA | quality assured |
| STR | single-tablet regimen |
| WHO | World Health Organization |

ARV medicines

| | |
|--------------|--|
| 3TC | lamivudine |
| ABC | abacavir |
| ATV | atazanavir |
| AZT | zidovudine |
| COBI | cobicistat |
| DRV | darunavir |
| DTG | dolutegravir |
| EFV | efavirenz |
| ETV | etravirine |
| EVG | elvitegravir |
| FTC | emtricitabine |
| LPV | lopinavir |
| LPV/r | lopinavir/ritonavir fixed-dose combination |
| r | ritonavir used as a booster |
| RAL | raltegravir |
| RPV | rilpivirine |
| RTV | ritonavir |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |
| XTC | either emtricitabine or lamivudine |

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