UNITAID

medicines patent pool

2014

Patents and licences on antiretrovirals: A snapshot

APRIL 2014

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UNITAID is hosted and administered by the World Health Organization

Note: this printing includes revisions from earlier versions of this report as noted on page 11.

World Health Organization

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Acronyms and abbreviations

3TC	lamivudine
ABC	abacavir
ARIPO	African Regional Industrial Property Organization
ARV(s)	antiretroviral(s)
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
d4T	stavudine
DRV	darunavir
DTG	dolutegravir
EAPO	Eurasian Patent Office
EFV	efavirenz
ETV	etravirine
EVG	elvitegravir
FDC(s)	fixed-dose combination(s)
FTC	emtricitabine
LPV	lopinavir
LPR/r	lopinavir/ritonavir fixed-dose combination
MPP	Medicines Patent Pool
MVC	maraviroc
NVP	nevirapine
OAPI	Organization Africaine de la Propriété Intellectuelle (African Intellectual Property Organization)
r	ritonavir
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization

Structure of the report

The report provides an overview of the patent landscape with respect to a select number of antiretroviral (ARV) medicines in developing countries as of April 2014. The focus is primarily on those ARVs that are recommended by the World Health Organization (WHO) as well as new ARVs that have either recently obtained regulatory approval or are in phase III clinical trials.

Part 1 provides a brief introduction to patents and licences and their effect on the market for ARVs. It introduces key concepts that will facilitate an understanding of the report. It also explains which data sources were used for the report and notes a number of disclaimers with regard to the information contained in the report.

Part 2 is the core of the report. It outlines the patent status and licensing status of each ARV in the 81 developing countries for which data are available. For each ARV the report indicates whether that ARV is included in fixed-dose combinations for which there may be patents. General conclusions are drawn in light of the data. The key purpose is to provide an overview of the patent landscape for each ARV and, in particular, to show in which countries market competition for a given ARV is possible in view of existing patents and licences.

Annex I is a summary table that provides a "snapshot" of ARV patents and licences in developing countries.

Annex II provides an overview of patents with respect to selected fixed-dose combinations.

Annex III summarizes the information that is currently publicly available on existing voluntary licences.

1. INTRODUCTION

1.1 Patents and antiretrovirals

A patent is a form of legal right granted by government to provide exclusivity over a new invention for a limited period of generally 20 years. During that period, the patent holder has the right to exclude others from making or selling the patented invention in the country (or countries) in which the patent was granted. Patents can be granted for different types of inventions, including a new medicine such as a new ARV. This section describes briefly how patents on ARVs are granted and introduces some key concepts that are important for understanding Part 2 and the annexes.

To obtain a patent on a new ARV, a pharmaceutical company or research organization must file a patent application at the national patent office of each country in which it would like to obtain exclusivity.[1] Each patent office is then responsible for examining the application[2] and making a decision on whether the invention described in the application fulfils the criteria for patentability. The patent examination process generally takes several years and during that period the patent application is considered to be pending. If the invention is considered to meet the patentability criteria, the patent office grants a patent which confers exclusive rights on the patent holder, thus effectively enabling the patent holder to prevent others from making, selling or using the patented product or process in the country for which the patent was granted. Some patent offices provide opportunities for third parties to submit patent oppositions during a specified period of time. Depending on national laws, this may happen prior to the grant of a patent or after a patent has been granted.

Patents may be granted for new products such as medicines, or for processes for manufacturing those medicines. Product patents may be granted on new molecules (often referred to as "base" patents or "compound" patents), or on specific forms or formulations of medicines (often referred to as "secondary" patents). The latter could include, for example, a particular salt form, an oral solution or tablet formulation of a given medicine, or a fixed-dose combination that combines more than one ARV compound into a single pill.[3] Some secondary patents (notably those related to liquid dosage forms) are relevant to paediatric formulations of a medicine but do not cover formulations for adults. In practice, new ARVs are generally covered by more than one patent or patent application.

The present report focuses on the compound patents for ARVs and a select number of secondary patents. In certain instances, information on several secondary patents on the same ARV has been combined for the sake of simplicity. This is notably the case for combination products or where there are multiple secondary patents/patent applications on a particular ARV. In such cases, the text and tables indicate whether at least one secondary patent has been granted, and if not whether at least one application was filed.

1.2 Patents as territorial rights

Patents are territorial rights, which means that they have effect only in the specific territory for which they were granted. Usually the territory is a country, but there are also some regional patent offices that grant patents for a group of countries. This is the case, for instance, of the *Organisation Africaine de la Propriété Intellectuelle* (OAPI), which grants patents that are valid in 16 countries in Africa. Other regional patent offices that are referred to in this report are the African Regional Intellectual Property Organization (ARIPO) and the Eurasian Patent Office (EAPO). The list of countries covered by these regional patent offices is provided in section 1.7.

1 Applicants have 12 months from the date on which they file the first patent application relating to an invention to file the same application in all the countries in which they wish to obtain protection, after which period it is no longer possible to do so. If an international patent application is filed using the Patent Cooperation Treaty administered by WIPO, the 12 months are effectively extended to 30 months.

2 It should be noted that a few patent offices (e.g. South Africa) do not undertake substantive examination of patent applications but examine only whether all the formalities have been met.

3 It should also be noted, however, that certain incremental inventions may not be patentable in some countries, as countries have set different thresholds for patentability.

As a result of the territorial nature of patents, an ARV may be patented in some countries but not in others. This may determine, for example, the extent to which there is market competition for a given ARV in different countries.

Despite the territorial nature of patents, it is important to note that the existence of patents on ARVs in the countries where most ARVs are currently manufactured (e.g. Brazil, China, India, South Africa, Thailand) may be sufficient to ensure exclusivity across developing countries to the patent holders. This is because patents in manufacturing countries could be used to prevent the production—and therefore prevent export—of the patented medicine into other countries. Thus, in order to understand whether there are patents that may have an impact on market competition in a country that imports ARVs, it is often necessary to review the patent status in countries that are likely to manufacture the ARVs as well as the importing country.

1.3 Licensing of patents on antiretrovirals

During the life of the patent, the patent holder may exercise the right to block others from manufacturing, selling or importing the patented product without consent. However, the patent holder may also give consent to other manufacturers to make or sell the product under certain conditions. This is generally done by means of a "voluntary licence" which sets out the conditions under which consent is given.

Licensing terms and conditions generally specify the countries in which a medicine may be made or sold; whether fixed-dose combinations can be developed; whether royalties are payable to the patent holder; which quality criteria need to be met by the licensee; and a wide range of other provisions that indicate what the licensee may and may not do.[4] Unfortunately, a detailed analysis of voluntary licences is not possible at this stage since, with the exception of the licences negotiated by the Medicines Patent Pool (MPP), the full terms and conditions of licences are confidential. Nevertheless, some general conditions are known and are included in this report.

In some cases, the patent holder may announce a commitment not to enforce its patents in certain countries; this may be done through a non-assert declaration, a commitment not to enforce, an immunity-from-suit agreement or similar mechanism. The practical effect of such commitments is often similar to that of licences and will be treated in this report as equivalent to licences. Nevertheless, the scope and certainty of these mechanisms varies.

As licences have become relatively common in the HIV field, it is important to look both at the existence of patents on a given ARV and at whether licences are available that cover a given country. Accordingly, this report includes licensing status information for each ARV.

The MPP negotiated some of the licences mentioned in this report. The MPP was established in 2010 with the support of UNITAID to negotiate public-health oriented and transparent voluntary licences on HIV medicines. The MPP's objective is to enhance access to more affordable HIV treatment in developing countries and to promote the development of new technologies such as fixed-dose combinations and formulations suitable for children.

In addition to voluntary licences, there are also instances in which a government may intervene without the consent of the patent holder and may issue a licence allowing the manufacture or importation of a given medicine despite the existence of a patent. This is called a compulsory licence and is allowed by most national patent laws.

4 Terms and conditions of licences may be onerous or access-friendly. For an overview of access-maximizing terms and conditions, see Park C et al. Voluntary licensing: an analysis of current practices and key provisions in antiretroviral voluntary licenses. Presentation at the 19th AIDS Conference, Washington, DC, 25 July 2012.
(http://www.medicinespatentpool.org/wp-content/uploads/Current-Practice-and-Key-Provisions-in-ARV-VLs.pdf, accessed 18 February 2014).

1.4 Patents and fixed-dose combinations

The advantages of fixed-dose combinations (FDCs), which combine several ARVs into a single formulation for the treatment of HIV, have been repeatedly highlighted.[5] It is important to note that patents on any individual ARV that is included in an FDC may have an impact on competition for the FDC as a whole. Thus, for an ARV manufacturer to be able to manufacture a given FDC and supply it to a given country, the manufacturer would need to ensure that in the countries of manufacture and sale there are no blocking patents on any of the ARVs included in the FDC or, if there are such patents, that the manufacturer has the necessary licences to do so.

In some instances, there are also patents on the FDCs themselves—e.g. on the combination of tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC), or abacavir (ABC) with lamivudine (3TC). These "combination patents" must be taken into consideration when analysing the patent landscape of a given treatment regimen. Annex II provides an overview of the patent and licence status of selected FDCs.

1.5 Methodology and data sources

This report was prepared by Esteban Burrone of the Medicines Patent Pool and Karin Timmermans of UNITAID, with input from Sandeep Juneja, Chan Park, Carmen Perez-Casas and Greg Perry. Claire Willmington helped with double-checking the data included in the report.

The main source of patent data for this report is the Patent Status Database for Selected HIV Medicines developed by the MPP. The database includes information collected from national and regional patent offices in developing countries. Covering 25 ARVs in 81 countries, it is the most comprehensive source of patent status data on ARVs available today.

Information on voluntary licences on ARVs was obtained from pharmaceutical company press releases and other public communications issued by the companies, or from the licences negotiated by the MPP. As noted above, however, public information on some of the voluntary licences is very limited.

1.6 Disclaimers

While the database used as the basis for this report is the most complete source of patent status data from developing countries, it is important to bear in mind its limitations. The database focuses on a select number of patents per ARV, and this may not be a comprehensive list—i.e. there may be other relevant patents that have not been identified and which therefore are not mentioned in this report.

Moreover, while the database is regularly updated, the patent status of a given ARV in a given country can change and data may therefore become outdated. It is advisable always to consult with the national or regional patent office for the most-up-to-date information on the status of a given patent or patent application.

With respect to expiry dates of the different ARVs, it is assumed in this report that most ARV patents expire in most countries 20 years after the filing of the patent application. It should be noted, however, that the exact date of expiry may vary from country to country as a result of differences in national patent laws or the existence of patent term extensions which are possible in some countries.

In addition, the database includes information on 81 developing countries (where more than 80% of people living with HIV reside) but it does not include all countries since data were not available to the MPP. A list of the countries covered by this report is provided below (section 1.7).

As concerns voluntary licences, the report is limited to the information that has been made publicly available by the licensors concerned, and may therefore be incomplete.

With respect to compulsory licences, in addition to those that have been widely publicized there are instances in which countries have issued letters to procurement agencies indicating that a medicine may

5 See, for example: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013.

be imported for the purpose of supplying the ministry of health, despite the existence of patents on the medicine. While some of these instances have been reported elsewhere[6], there is a lack of publicly available information on this practice. Therefore, it has not been possible to include them in this report.

1.7 Countries covered

The following countries are covered by this report: Albania, Algeria, Argentina, ARIPO member countries, Bolivia, Bosnia and Herzegovina, Brazil, China, Colombia, Costa Rica, Cuba, Dominican Republic, EAPO member countries, Egypt, Georgia, Guatemala, Honduras, India, Indonesia, Jordan, Malaysia, Mexico, Mongolia, Montenegro, Morocco, Nicaragua, OAPI member countries, Pakistan, Panama, Paraguay, Peru, Philippines, South Africa, Sri Lanka, Thailand, Turkey, Ukraine, Uzbekistan, Venezuela and Viet Nam.

ARIPO member countries are: Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, United Republic of Tanzania, Zambia and Zimbabwe.

EAPO member countries are: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan and Turkmenistan.

OAPI member countries are: Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Guinea, Guinea-Bissau, Mali, Mauritania, Niger, Senegal and Togo.

6 't Hoen E, The global politics of pharmaceutical monopoly power. Diemen; AMB Publishers; 2009.

2. OVERVIEW OF PATENTS BY ANTIRETROVIRAL

2.1 Abacavir (ABC)

Abacavir is recommended by WHO as a component of first- and second-line treatment regimens for infants and children.

Patent status

The compound patent on abacavir expired in 2010 in all jurisdictions for which recent data are available. There are, however, other patents on forms and formulations of abacavir that may affect the market for abacavir and abacavir-containing formulations.

A patent on the hemisulfate salt is expected to expire in 2018. According to available information, the patent was granted in Argentina, ARIPO member countries, China, EAPO member countries, Egypt, Georgia, Guatemala, Honduras, Indonesia, Jordan, Malaysia, Mexico, Morocco, Nicaragua, OAPI member countries, Pakistan, Panama, Peru, Philippines, South Africa, Sri Lanka, Turkey and Ukraine, and is pending in Algeria, Brazil, Thailand, Tunisia and Venezuela.

A patent on the paediatric oral solution, which is expected to expire in 2019, was granted in Argentina, ARIPO member countries, Colombia, EAPO member countries, India, Indonesia, Malaysia, Morocco, Mexico, Peru, Philippines, South Africa, Sri Lanka and Turkey, and is pending in China, Egypt and Thailand.

Licensing status

The patent holder has committed to licensing abacavir to interested ARV manufacturers for all low-income countries, least-developed countries and sub-Saharan Africa (representing at the time of announcement 69 countries).

Patents on paediatric formulations of abacavir and its combination with lamivudine (3TC) for paediatric use have been licensed to the MPP with a geographical coverage of 118 countries. The licence also allows sale in other countries where there are no patents in force.[7] In addition, a licence on abacavir paediatric formulations has been granted by the patent holder directly to one manufacturer.

In 2012, Indonesia issued a compulsory licence on abacavir and Ecuador issued a compulsory licence on the combination patent referred to below.

Combinations

Combinations of abacavir have been developed with lamivudine, and with lamivudine and zidovudine, and are sold by several generic manufacturers. Patents on the combination(s) exist in several jurisdictions, including ARIPO member countries, Brazil, China, EAPO member countries, Georgia, Malaysia, Mexico, OAPI member countries, Pakistan, Philippines and South Africa, and are pending in Sri Lanka and Turkey.

Conclusion

While the compound patent for abacavir has expired, patents on the hemisulfate salt, the paediatric formulation and the combination of abacavir with lamivudine have been widely granted in many jurisdictions and could limit market competition for abacavir in certain countries not covered by the voluntary licences.

7 The full text of the licence is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.2 Atazanavir (ATV)

Atazanavir (boosted with ritonavir) is recommended by WHO as a component of second-line treatment regimens in adults.

Patent status

The compound patent on atazanavir is exclusively licensed to Bristol-Myers Squibb by Novartis. Its expected expiry date is 2017. According to available information, the compound patent is currently in force in the following low- or middle-income countries: Argentina, Brazil, China, Malaysia, Mexico, Pakistan, Philippines and South Africa. The patent application is pending in India and Thailand.

The patent on the bisulfate salt is also likely to be relevant to the production of atazanavir. Its expected expiry date is 2018 and has been granted in the following low- or middle-income countries: Argentina, China, Egypt, Georgia, Indonesia, Malaysia, Mexico, Pakistan, Peru, Philippines, South Africa, Thailand, Turkey and Ukraine.

Licensing status

In December 2013, atazanavir was licensed to the MPP. The licence has a geographical scope of 110 countries and contains provisions that do not impede sale to additional countries where there is no infringement of patents on atazanavir under certain circumstances.[8] Prior to that, immunity from suit agreements were in place with three generic manufacturers with a geographical scope comprising sub-Saharan Africa and India (50 countries).

A bilateral technology transfer agreement has been signed with a Brazilian company and includes a licence for Brazil.

Combinations

The only fixed-dose combination containing atazanavir that currently has regulatory approval is atazanavir/ritonavir (ATV/r), for which there is currently only one quality-assured manufacturer (though other manufacturers are known to have the product in the pipeline).

Conclusion

Market competition for atazanavir is likely to increase in countries covered by the new MPP licence or in countries where there are no patents in force. In countries outside the scope of the MPP licence and in which there are patents on atazanavir, market competition may be delayed until patent expiry. Patents on ritonavir will also probably affect the sale of ATV/r in certain jurisdictions.

8 The full text of the licence is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.3 Cobicistat (COBI)

Cobicistat was approved by the United States Food and Drug Administration in 2012 as part of the combination tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat (TDF/FTC/EVG/COBI), which is also known as the Quad.

Patent status

The compound patent on cobicistat is expected to expire in 2027. It has been granted in OAPI member countries and in Ukraine. It is pending in Argentina, ARIPO member countries, Brazil, China, EAPO member countries, India, Indonesia, Mexico, South Africa, Thailand and Viet Nam. Other patents on cobicistat are also pending in these countries and perhaps in other countries. However, there is limited information on the status of these other patents in developing countries.

Licensing status

Voluntary licences on cobicistat have been granted in relation to 112 countries (nine of them on a semi-exclusive basis to three different companies). The licence granted to the MPP covers 103 countries and has so far been sublicensed to six companies.[9]

Combination

Cobicistat has been developed as part of the combination TDF/FTC/EVG/COBI and is currently under development as a booster for atazanavir and darunavir and in the combinations TAF/FTC/DRV/COBI and TAF/FTC/EVG/COBI.

Conclusion

While no generics are yet on the market, competition for combinations containing cobicistat is likely to occur in countries covered by the voluntary licences.

9 The full text of the licence is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.4 Darunavir (DRV)

Darunavir (boosted with ritonavir) is recommended by WHO as a component of third-line treatment regimens and as an alternative in second-line regimens for adults.

Patent status

The compound patent on darunavir generally expired in August 2013 in jurisdictions in which it had been granted.

A method of use patent is not in force in developing countries.

Patents on the pseudopolymorph and/or on the combination with ritonavir have been granted in Albania, ARIPO member countries, China, EAPO member countries, Mexico, Philippines, South Africa and Turkey and are pending in Argentina, Brazil, India, Indonesia, OAPI member states and Viet Nam.

Licensing status

A commitment not to enforce patents on darunavir in sub-Saharan Africa and least-developed countries has been announced by the patent holder. In addition, a licence was granted to one manufacturer for sale of the medicine in India.

Combinations

While darunavir requires boosting with ritonavir (or potentially with cobicistat) there are currently no such quality-assured combinations on the market. Clinical trials are ongoing for DRV/COBI and DRV/TAF/FTC/COBI combinations.

Conclusion

There appear to be limited patents on darunavir in developing countries. The compound patent has expired. Secondary patents, such as those on the pseudopolymorph or on combinations, may potentially delay competition in countries where they have been granted unless they are covered by the commitment not to enforce patents. Patents on ritonavir will also probably affect the sale of DRV/r in certain jurisdictions.

2.5 Dolutegravir (DTG)

Dolutegravir was approved by the United States Food and Drug Administration in 2013.

Patent status

The compound patent for dolutegravir is expected to expire in 2026, has been granted in Algeria, Colombia, EAPO member countries, Indonesia, Morocco, Philippines, South Africa and Ukraine, and is pending in Brazil, China, Egypt, India, Malaysia, Mexico and Viet Nam.

Licensing status

In April 2014, the MPP and ViiV Healthcare announced licences on adult and paediatric formulations of dolutegravir. The paediatric licence includes 121 countries. The adult license includes all countries in sub-Saharan Africa, least-developed countries, low-income countries, Egypt, India, Indonesia, Philippines, Turkmenistan and Viet Nam. In addition, the licences allow for the sale of generic versions of dolutegravir outside the licensed countries where there are no patents in force.

Combinations

A combination containing DTG + ABC/3TC, which is known as 572-Trii, is in phase III clinical trials. In addition to the patents on dolutegravir and abacavir, patents on the combinations ABC/3TC and ABC/3TC/DTG may have an impact on the use of a regimen consisting of ABC/3TC and DTG. The MPP licence on dolutegravir also covers combinations containing abacavir and dolutegravir with the same geographical scope.

Conclusion

Following the licence between the MPP and ViiV, market competition for dolutegravir is likely to take place in countries covered by the licence as well as those countries in which dolutegravir is not patented.

2.6 Efavirenz (EFV)

Efavirenz is recommended by WHO as a component of first-line treatment regimens for adults and as a component of first- and second-line treatment regimens for children over three years of age.

Patent status

The compound patent on efavirenz is likely to have expired in or around August 2013 in most countries. There are some exceptions where it is expected to expire later as a result of patent term extensions (for instance, expiry in Ukraine is expected in 2018). According to available information, the compound patent was in force in Argentina, China, Dominican Republic, Indonesia, Mexico, Pakistan (process patent only), South Africa, Thailand and Ukraine but is likely to have expired in most of these countries.

Licensing status*

A number of South African manufacturers have obtained a licence for production of efavirenz in South Africa and sale to 10 neighbouring countries. Compulsory licences on efavirenz have been issued in Brazil, Indonesia and Thailand.

Combinations

Combinations of efavirenz with TDF/FTC and with TDF/3TC have been developed and are recommended by WHO as preferred first-line regimens. Bristol-Myers Squibb and Gilead Sciences jointly own patents, and patent applications on the combination with TDF/FTC, which have been granted in EAPO member states, South Africa and Turkey are also pending in Argentina, Brazil, China, India, Mexico, Thailand and Venezuela.

Conclusion

The compound patent on efavirenz was in force in several countries and probably expired in most of them in August 2013. Several quality-assured generics are on the market and, with few exceptions, there should in principle be no intellectual property-related constraints to market competition for efavirenz as a single agent. Patents and patent applications on TDF/FTC/EFV may delay market competition for this combination in certain countries (see Annex II).

*Note: These details revised from previous printing of this report.

2.7 Elvitegravir (EVG)

Elvitegravir was approved by the United States Food and Drug Administration in 2012 in the context of the approval of the combination TDF/FTC/EVG/COBI (also known as the Quad).

Patent status

The compound patent on elvitegravir is expected to expire in 2023 and was granted in Albania, China, Colombia, India, Malaysia, Mexico, Peru, Philippines and South Africa. It is pending in Argentina, Brazil, Indonesia, Venezuela and Viet Nam.

The patent on the crystal form is granted in China, Colombia, Malaysia, Mexico, Philippines and South Africa and is pending in Argentina, Bolivia, Brazil, Thailand and Venezuela.

Licensing status

Voluntary licences on elvitegravir have been granted in relation to 109 countries (nine of them on a semi-exclusive basis to three companies). The licence granted to the MPP covers 100 countries and has so far been sublicensed to six companies.[10]

Combination

Elvitegravir has been developed in combination with TDF, FTC and COBI.

Conclusion

While no generics are yet on the market, several manufacturers are developing elvitegravir. Once quality-assured versions are available, competition is likely to take place in the countries covered by the voluntary licences.

10 The full text of the licence is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.8 Emtricitabine (FTC)

Emtricitabine is recommended by WHO as a component of first-line treatment regimens and as an alternative in second-line regimens for adults. It is also an alternative component in first- and second-line regimens for children. It is generally considered to be interchangeable with lamivudine.[11]

Patent status

The compound patent on emtricitabine expired in 2010. Other patents have also expired and are therefore no longer in force in most developing countries. However, patents on combinations containing emtricitabine remain in force in many jurisdictions.

Licensing status

The patent holder has issued "covenants not to sue" on emtricitabine with a geographical scope of 112 countries. The covenant not to sue granted through the MPP is publicly available.[12]

Combinations

The following fixed-dose combinations include emtricitabine: TDF/FTC, TDF/FTC/EFV, TDF/FTC/RPV and TDF/FTC/EVG/COBI. Patents and patent applications on some of these combinations have been filed (and in a few cases granted) in several developing countries (see Annex II).

Conclusion

Given the expiry of the compound patent on emtricitabine, and covenants not to sue that cover certain secondary patents, there is already strong market competition for ARV regimens containing emtricitabine. Nevertheless, patents on the combinations (or on any of the other individual ARVs in those combinations) may delay market competition for the combinations containing emtricitabine in countries not covered by the licences.

11 Technical update on treatment optimization. Pharmacological equivalence and clinical interchangeability of lamivudine and emtricitabine: a review of current literature. Geneva: World Health Organization; 2012.

12 The full text of the covenant not to sue is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.9 Etravirine (ETV)

Etravirine is recommended by WHO as a component of third-line treatment regimens.

Patent status

The compound patent on etravirine is expected to expire in 2019. It has been granted in Argentina, ARIPO member countries, Brazil, China, EAPO member countries, India, Malaysia, Mexico, OAPI member countries, Philippines, South Africa, Sri Lanka, Turkey, Ukraine and Viet Nam, and appears to be pending in Indonesia and Pakistan.

Patents on novel forms of etravirine, expiring in 2026, have been granted in Albania, Mexico and Turkey and are pending in Brazil, China and India.

Licensing status

There are currently no voluntary licences for the manufacturing of generic etravirine. There is a distribution and packaging agreement with one company (Aspen Pharma) for sub-Saharan Africa and least-developed countries.

Combinations

There are no fixed-dose combinations containing etravirine on the market.

Conclusion

There are no pharmaceutical companies manufacturing generic etravirine and, given the patent coverage in key manufacturing countries, it is likely that a licence would be required for that to happen. Etravirine is widely patented in developing countries.

2.10 Lamivudine (3TC)

Lamivudine is recommended by WHO as a component of all first- and second-line treatment regimens. It is generally considered interchangeable with emtricitabine.[13]

Patent status

The compound patent on lamivudine expired in 2010. Other patents on lamivudine, while granted in many developing country jurisdictions, do not appear to affect competition for lamivudine in the market.

Licensing status

In 2010, the patent holder announced the intention to license all of its current and pipeline products with a geographical scope that includes sub-Saharan Africa, least-developed countries and low-income countries (69 countries in total). Nevertheless, given the expiry of the key patents on this ARV, licences appear to be no longer required by ARV manufacturers wishing to sell generic versions in most (if not all) developing-country jurisdictions.

A licence on the combination of abacavir and lamivudine for paediatric use was granted to the MPP in February 2013 and covers 118 countries.

Combinations

There are several combinations of lamivudine that have received regulatory approval, many of which are recommended by WHO. These include ABC/3TC, ABC/3TC/AZT, TDF/3TC and TDF/3TC/EFV. Patents on the ABC/3TC combination have been granted in several jurisdictions, including ARIPO member countries, Brazil, China, EAPO member countries, Georgia, Malaysia, Mexico, OAPI member countries, Pakistan, Philippines and South Africa, and are pending in Sri Lanka and Turkey.

Conclusion

Market competition for lamivudine, and for most fixed-dose combinations containing lamivudine, is strong with several manufacturers having quality-assured formulations. Combination patents have been granted in some countries and may delay market competition for those combinations.

13 Technical update on treatment optimization. Pharmacological equivalence and clinical interchangeability of lamivudine and emtricitabine: a review of current literature. Geneva: World Health Organization; 2012.

2.11 Lopinavir (LPV)

Lopinavir (boosted with ritonavir, LPV/r) is recommended by WHO as a component of second-line treatment regimens for adults and children, and as a component of the first-line treatment regimen for children under three years.

Patent status

The compound patent for lopinavir is expected to expire in 2017 and has been granted in Argentina, China, Colombia, Mexico, Philippines, South Africa and Thailand.

Since lopinavir is available only in combination with ritonavir, patents on formulations of lopinavir/ritonavir are also very important and are outlined under "Combinations" below.

Licensing

No voluntary licences have been issued on lopinavir to date. The MPP and AbbVie are in negotiations regarding paediatric formulations of LPV/r. Some countries (e.g. Ecuador) have issued compulsory licences on ritonavir or on the combination of lopinavir with ritonavir (e.g. Indonesia and Thailand).

Combinations

A patent on the LPV/r soft gel capsules, expiring in 2017, was granted in Argentina, Brazil, China, Indonesia, Mexico, Philippines, South Africa and Turkey, and is pending in Pakistan and Thailand.

Two patents on LPV/r tablet formulations, which expire in 2024 and 2026 respectively, have been granted in Albania, Bosnia, EAPO member countries, Georgia, Guatemala, Mexico, Montenegro, Peru, Philippines, South Africa, Sri Lanka, Turkey, Ukraine and Viet Nam, and are pending in Brazil, China and Dominican Republic.

Conclusion

Patents on lopinavir, ritonavir and on the capsules and tablets of LPV/r have been granted or are pending in many jurisdictions. There are currently four quality-assured generic suppliers of LPV/r adult formulations and two of paediatric formulations. However, in the absence of voluntary licences, competition among manufacturers may be limited to countries where there are no patents or where a compulsory licence has been issued.

2.12 Maraviroc (MVC)

Maraviroc was approved by the United States Food and Drug Administration in 2007. It is not currently recommended by WHO.

Patent status

The compound patent on maraviroc is expected to expire in 2019 in most jurisdictions. It has been granted in Albania, Argentina, ARIPO member countries, Bolivia, Cuba, EAPO member countries, Egypt, Georgia, Guatemala, India, Malaysia, Mexico, Montenegro, Morocco, OAPI member countries, Panama, Peru, Philippines, South Africa, Turkey, Ukraine, Uzbekistan and Viet Nam. According to the latest available data, the patent is also pending in Algeria, Bosnia, Indonesia, Paraguay and Sri Lanka.

The patent on the crystal form of maraviroc, which is expected to expire in 2021, has been granted in Albania, Argentina, ARIPO member countries, Bosnia, China, Colombia, Cuba, EAPO member countries, Egypt, Georgia, Guatemala, India, Mexico, Mongolia, Montenegro, Morocco, OAPI member countries, Panama, Peru, Philippines, South Africa, Turkey, Ukraine and Uzbekistan. The patent is also pending in Bolivia, Brazil, Thailand and Viet Nam.

Licensing status

In July 2010, the patent holder announced the intention to license all its current and pipeline products with a geographical scope of all sub-Saharan Africa, low-income countries and least-developed countries (at the time 69 countries). However, no specific licences on maraviroc have been announced to date and there are no generic products on the market as yet.

Combinations

There are currently no fixed-dose combinations containing maraviroc.

Conclusion

Maraviroc is very widely patented in developing countries and there is currently no generic on the market. If the ARV were included in treatment recommendations and demand were to increase, market competition for maraviroc would probably be limited to the countries for which a commitment to license has been announced.

2.13 Nevirapine (NVP)

Nevirapine is recommended by WHO as a component of alternative first-line treatment regimens for adults, and as a component of alternative first- and second-line treatment regimens for children and infants.

Patent status

The compound patent on nevirapine expired in 2010 in most (if not all) jurisdictions.

The patent on the hemihydrate formulation used for children is expected to expire in 2018. It has been granted in Brazil, China, Malaysia, Mexico, Montenegro, Peru, Philippines, South Africa, Turkey, Ukraine, Uzbekistan and Viet Nam. On the basis of available information, the patent appears to be pending in Egypt, Indonesia, Pakistan and Thailand, and was rejected in India following a patent opposition.

The patent on the extended release formulation was granted in Morroco, South Africa and Ukraine. It appears to be pending in Argentina, China, Colombia, EAPO member countries, Egypt, India, Mexico, Pakistan, Peru, Philippines, Venezuela and Viet Nam.

Licensing status

The patent holder has a policy of issuing non-assert declarations for some 78 countries to any manufacturer that obtains WHO prequalification for nevirapine. This covers India, all of Africa, low-income countries and least-developed countries.

Combinations

Nevirapine has been developed in combination with AZT/3TC and d4T/3TC. No patents have been identified on these combinations.

Conclusion

With the compound patent on nevirapine having expired, patents do not appear to be a constraint on market competition for nevirapine in developing countries. In light of existing patents on the paediatric formulation and the extended release formulation, there may be restrictions on competition for these specific formulations outside the countries covered by the non-assert declarations.

2.14 Raltegravir (RAL)

Raltegravir is recommended by WHO as a component of third-line treatment regimens.

Patent status

The compound patent on raltegravir is expected to expire in developing countries in or around 2022. According to available information, the patent was granted in Albania, China, Colombia, Georgia, India, Mexico, Montenegro, Philippines, South Africa, Turkey, Ukraine, Uzbekistan and Viet Nam, and is pending in Brazil.

The patent on the potassium salt is expected to expire in 2025 and was granted in Belarus, China, Colombia, Georgia, Kazakhstan, Malaysia, Mexico, Mongolia, Morocco, Philippines, South Africa, Turkey and Ukraine. Patent applications appear to be pending in Albania, Argentina, Bosnia, Brazil, Costa Rica, India, Nicaragua, Panama, Pakistan, Thailand and Viet Nam.

Licensing status

The patent holder has granted voluntary licences on raltegravir to two manufacturers, neither of which has a quality-assured product on the market as yet, although one manufacturer has obtained approval from the Expert Review Panel (ERP) of the Global Fund for time-limited use. Detailed terms and conditions of the licences are not publicly available but the licences are known to cover sub-Saharan African and low-income countries (a total of approximately 58 countries). A bilateral technology transfer agreement has been signed between the patent holder and a Brazilian company with a licence for Brazil.

Combinations

There are currently no quality-assured fixed-dose combinations containing raltegravir.

Conclusion

Raltegravir is widely patented in developing countries, including in major countries of manufacture of quality-assured ARVs (e.g. India). Once manufacturers develop quality-assured generic versions of the product, their ability to supply them would probably be limited to the countries covered by licences.

2.15 Rilpivirine (RPV)

Rilpivirine was approved by the United States Food and Drug Administration in 2011.

Patent status

The compound patent on rilpivirine is expected to expire in 2022. The patent has been granted in Albania, Argentina, ARIPO member countries, China, EAPO member countries, India, Mexico, OAPI member countries, Panama, Philippines, South Africa, Sri Lanka, Turkey and Ukraine, and appears to be pending in Brazil, Egypt, Jordan, Malaysia, Pakistan, Venezuela and Viet Nam.

A patent on the salt form, expiring in 2025, has been granted in ARIPO member countries, EAPO member countries, Philippines, South Africa, Turkey and Ukraine, and is pending in Brazil, China, Mexico and Viet Nam.

Licensing status

Voluntary licences for RPV have been granted to five manufacturers covering 112 countries. The detailed terms and conditions are not publicly available.

Combinations

A combination of rilpivirine with TDF/FTC was developed and obtained regulatory approval in 2011.

Conclusion

While no quality-assured generics are on the market as yet, market competition for this ARV will be possible in the countries covered by the voluntary licence.

2.16 Ritonavir (RTV or r)

Ritonavir is recommended by WHO as a booster for atazanavir, lopinavir and darunavir.

Patent status

The compound patent on ritonavir was due to expire at the end of 2013. It is currently in force only in Mexico and Philippines among countries for which data was available for this report. Nevertheless, there are other patents that are also relevant to the production and sale of ritonavir.

A patent on the polymorph, which expires in 2019, has been granted in Argentina, Malaysia, Mexico, Philippines and Turkey. It appears to be pending in China, Indonesia, and Thailand.

A patent on the tablet formulation, expiring in 2024, was granted in Albania, Bosnia, EAPO member countries, Mexico, Montenegro, South Africa, Sri Lanka, Turkey, Ukraine and Viet Nam, and appears to be pending in Brazil and China.

Licensing

No voluntary licences have been granted on ritonavir to date. The MPP and AbbVie are in negotiations regarding a licence for ritonavir paediatric formulations. Compulsory licences were granted on ritonavir or its combination with lopinavir in Ecuador, Indonesia and Thailand.

Combinations

Currently available combinations that include ritonavir are LPV/r and ATV/r. Patents on ritonavir and on LPV/r tablets are likely to delay competition in certain markets (see details under lopinavir).

Conclusion

Since ritonavir has not been patented in key producing countries like India, there are several generic suppliers of ritonavir on its own or in combination with protease inhibitors. Nevertheless, in the absence of voluntary licences, competition among manufacturers may be limited to countries where there are no patents or where a compulsory licence has been issued.

2.17 Tenofovir alafenamide fumarate (TAF)

Tenofovir alafenamide fumarate is a pro-drug of tenofovir; it is currently in phase III clinical trials.

Patent status

The compound patent on tenofovir was filed by the Czech Academy of Science in 1985 and has expired in most (if not all) jurisdictions where it was granted.

The patent on this tenofovir pro-drug is expected to expire in 2021. The patent has been granted in ARIPO member countries, China, India, South Africa and Ukraine and, according to the information that is currently available, is pending in Brazil, Mexico, OAPI member countries and Viet Nam.

Licensing status

Tenofovir alafenamide fumarate is in phase III clinical trials and has not yet been licensed to ARV manufacturers. Nevertheless, the MPP and Gilead are currently in negotiations regarding a licence on adult and paediatric formulations of this pro-drug.

Combinations

Tenofovir alafenamide fumarate is being developed in combination with FTC/EVG/COBI and FTC/DRV/COBI.

Conclusion

Patents on tenofovir alafenamide fumarate have been granted in many of the countries currently producing quality-assured ARVs (e.g. China, India, South Africa). If and when tenofovir alafenamide fumarate obtains regulatory approval, market competition among ARV manufacturers is likely to occur in countries covered by voluntary licences that may be issued by the patent holder.

2.18 Tenofovir disoproxil fumarate (TDF)

Tenofovir disoproxil fumarate is recommended by WHO as a component of the first-line treatment regimen and as an alternative component of second-line regimens for adults. It is also recommended as a component of alternative first-line and second-line treatment regimens for children over three years of age.

Patent status

The compound patent on tenofovir was filed by the Czech Academy of Science in 1985 and has expired in jurisdictions where it was granted.

The patents on the disoproxil ester and the fumarate salt are due to expire in 2017 and 2018 respectively. On the basis of available information, these patents appear to have been only granted in China, Indonesia and Mexico and were either not filed, opposed or rejected in most other low- or middle-income countries. A process patent has been granted in India.

Licensing status

Tenofovir disoproxil fumarate has been licensed to several ARV manufacturers with a geographical scope of 112 countries. In 2011, it was licensed to the MPP and the detailed terms and conditions of that licence are publicly available. As a result of the unbundling provisions in the MPP/Gilead licence, generic manufacturers that have taken the MPP licence and made use of that flexibility have been able to supply additional developing countries in which tenofovir disoproxil fumarate is not patented.[14]

Indonesia issued a compulsory licence on tenofovir and its combinations with FTC and FTC/EFV in 2012.

Combinations

There are several approved combinations that contain tenofovir, such as TDF/FTC, TDF/3TC, TDF/3TC/EFV, TDF/FTC/EFV, TDF/FTC/EVG/COBI and TDF/FTC/RPV. Patent applications relating to one or more of these combinations have been granted in Albania, ARIPO member states, China, EAPO member states, Indonesia, Malaysia, Mexico, OAPI member states, Philippines, South Africa, Turkey, Ukraine and Viet Nam, and are pending in Argentina, Brazil, India, OAPI member states, Philippines, Thailand and Venezuela. While there are licences or "covenants not to sue" on TDF, FTC, EVG, COBI and RPV, the sale of generic versions of the combinations may be delayed outside countries covered by these as a result of patents on the individual compounds or on the combinations (see Annex II).

Conclusion

With limited exceptions (notably China and Mexico) there appears to be robust market competition for tenofovir today in most low- and middle-income countries. Market competition may be limited for some generic TDF-containing combinations in countries outside the 112 licensed territories.

14 The full text of the licence is available on the Medicines Patent Pool website at www.medicinespatentpool.org.

2.19 Zidovudine (AZT)

Zidovudine is recommended by WHO as a component of the second-line treatment regimen for adults and first-line treatment regimens for children less than three years of age. It is also a component of alternative first-line treatment regimens for all age groups.

Patent status

The compound patent on zidovudine expired in 2006. A patent on the combination with lamivudine expired in 2012 and the patent on the zidovudine/lamivudine tablet formulation was withdrawn or allowed to lapse in most (if not all) developing countries for which recent data are available.

Licensing status

The patent holder has committed to licensing all its ARVs to interested manufacturers for a geographical coverage of 69 countries, including all low-income countries, least-developed countries and sub-Saharan Africa. Nevertheless, given the expiry and withdrawal of most of the patents on this ARV, licences are no longer required by ARV manufacturers to sell generic versions in most (if not all) developing countries.

Combinations

Zidovudine is available as a combination with lamivudine with ABC/3TC and with 3TC/NVP. As noted above, the key patents on the combination have either expired or appear to have been withdrawn.

Conclusion

As zidovudine was the first ARV to obtain regulatory approval, the main patents have by now expired or have been withdrawn by the patent holder. Market competition for zidovudine, and for combinations that contain zidovudine, is strong with several manufacturers having quality-assured versions.

3. CONCLUSION

As can be seen from the preceding analysis, older ARVs such as zidovudine, emtricitabine, lamivudine and nevirapine are generally off patent. The main patents for these products, where they had been granted, have now generally expired or are close to expiry. Markets for these products tend to be competitive and there are several quality-assured manufacturers that are in a position to supply most (if not all) developing-country markets. Nevertheless, patents or patent applications on some formulations (e.g. extended release nevirapine) or fixed-dose combinations with other ARVs (e.g. TDF/FTC/RPV or ABC/3TC) may exist in certain countries and could delay competition in countries for which licences are not currently available.

Newer ARVs, including those that are currently in the development pipeline, tend to be more widely patented in developing countries, though there is wide variation between ARVs. Patents on some of these ARVs (such as atazanavir, dolutegravir, elvitegravir, etravirine, lopinavir, raltegravir and rilpivirine) have been filed in a significant number of developing countries and, where they have been granted, will likely remain in force for several years before they expire. For such ARVs, it is likely that market competition will take place only in countries where there is no patent or where licences have been issued. In addition, the conditions in voluntary licences can vary significantly and may determine whether and where generic ARV manufacturers are able to supply. In light of the above, the likelihood of competition is very country- and product-specific.

From the preceding analysis, it can furthermore be noted that:

- With respect to the ARVs that have been recommended by WHO for first-line adult treatment in the 2013 consolidated treatment guidelines, market competition is likely to be possible in the vast majority of developing countries. The few exceptions are cases where tenofovir or efavirenz are patented and are not covered by licences, and/or where there are patents pending or granted for the combinations of tenofovir with emtricitabine or tenofovir with emtricitabine and efavirenz.[15]
- As concerns second-line adult treatment, the situation is more complex, with patents granted in several developing countries for atazanavir, lopinavir and ritonavir, and licences issued for atazanavir. Third-line medicines etravirine and raltegravir are widely patented, including in key countries of manufacture, and there are some secondary patents on darunavir; licences appear to be limited (raltegravir) or non-existent (etravirine).
- With respect to paediatric treatment, a number of recommended ARVs could face patent-related delays to competition. Given the need for the development of and widespread access to better-adapted paediatric formulations, more extensive licensing would be important.
- As concerns ARVs that are in late-stage clinical development or have only recently received regulatory approval (such as cobicistat, dolutegravir, elvitegravir, rilpivirine and tenofovir alafenamide fumarate), patents appear to have been granted or are pending in several developing countries, including most countries with ARV manufacturing capacity. As a result, licences are likely to be important in providing the conditions for the competitive procurement of new regimens containing those ARVs.

On the basis of the available data, the likelihood that market competition can take place for patented ARVs appears to be lowest in certain upper- and lower-middle-income countries outside sub-Saharan Africa. It is highest in low-income countries, least-developed countries, certain other middle-income countries, and countries in sub-Saharan Africa, where licences are more widely available. However, it is important to reiterate that patents in manufacturing countries, such as India, can affect the availability of ARVs in importing countries, even in the absence of local patents in the importing country.

15 Note that these patents or patent applications probably do not cover the combinations with lamivudine instead of emtricitabine. However, for certainty on this issue, a detailed analysis of the claims granted in each country would be required.

Annex I. Summary table on ARV patents and licences[16]

	Albania	Algeria	Argentina	ARIPO	Armenia	Azerbaijan	Belarus	Bolivia	Bosnia	Brazil	China	Colombia	Costa Rica	Cuba	Dominican Republic	Egypt	Georgia	Guatemala	Honduras	India	Indonesia	Jordan	Kazakhstan	
ABC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**ABC**
- 2nd	•	F	G	G	G	G	G	-	•	F	G	G	-	-	-	G	G	G	G	G	G	G	G	**- 2nd**
ATV	-	-	G	-	-	-	G	-	-	G	G	-	-	-	-	•	-	-	-	F	-	•	-	**ATV**
- 2nd	-	•	G	-	-	-	-	-	-	F	G	-	-	-	-	G	G	-	-	F	G	•	-	**- 2nd**
COBI	-	•	F	F	F?	F	F	-	-	F	F	-	•	-	-	•	-	-	-	F	F	•	F	**COBI**
- 2nd	-	•	F	F	F?	F	F	-	-	•	F	-	•	-	-	•	-	-	-	F	F	•	F	**- 2nd**
DRV	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	•	-	-	-	-	-	-	-	**DRV**
- 2nd	G	•	F	G	G	G	G	-	-	F	G	-	-	-	-	•	-	-	-	F	F	•	G	**- 2nd**
DTG	-	G	-	-	G	G	G	-	-	F	F	G	-	-	-	F	-	-	-	F	G	•	G	**DTG**
- 2nd	-	-	-	-	•	•	•	-	-	•	F	-	-	-	-	-	-	-	-	F	F	•	-	**- 2nd**
EFV *	-	F	G	-	-	-	•	-	-	-	G	-	-	-	-	•	-	-	-	-	G	•	-	**EFV ***
- 2nd	-	•	F	-	G	G	G	-	-	F	F	-	-	-	-	•	-	-	-	F	-	•	G	**- 2nd**
ETV	-	•	G	G	G	G	G	-	-	F	G	-	-	-	-	•	-	-	-	G	F	•	G	**ETV**
- 2nd	G	•	-	-	-	-	•	-	-	F	F	-	-	-	-	•	-	-	-	F	•	•	•	**- 2nd**
EVG	G	•	F	-	-	-	•	-	-	F	G	G	-	-	-	•	-	-	-	G	F	•	•	**EVG**
- 2nd	-	•	F	-	F	F	F	F	-	F	G	G	-	-	-	•	-	-	•	F	•	•	F	**- 2nd**
LPV	-	•	G	-	-	-	•	-	-	-	G	G	-	-	-	•	-	-	-	-	-	•	-	**LPV**
- 2nd	G	•	G	-	G	G	G	-	G	G	G	-	-	-	F	•	G	G	-	-	-	•	G	**- 2nd**
MVC	G	F	G	G	G	G	G	G	F	-	-	-	-	G	-	G	G	G	-	G	F	•	G	**MVC**
- 2nd	G	•	G	G	G	G	G	F	G	F	G	G	-	G	-	G	G	G	-	G	•	•	G	**- 2nd**
NVP	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	•	-	**NVP**
- 2nd	-	•	F	-	F?	F	F	-	-	G	G	F	-	-	-	F	-	-	-	F	F	•	F	**- 2nd**
RAL	G	•	-	-	-	-	•	-	-	F	G	G	-	-	-	•	G	-	-	G	•	•	-	**RAL**
- 2nd	F	•	F	-	-	-	G	-	F	F	G	G	F	-	-	•	G	-	-	F	•	•	G	**- 2nd**
RPV	G	•	G	G	G	-	•	-	-	F	G	-	-	-	-	F	-	-	-	G	•	F	•	**RPV**
- 2nd	-	•	F	G	G	G	G	-	-	F	F	-	•	-	-	•	-	•	•	-	•	•	G	**- 2nd**
RTV	-	•	-	-	-	-	-	-	-	-	-	-	-	-	-	•	-	-	-	-	-	•	-	**RTV**
- 2nd	G	•	G	-	G	G	G	-	G	F	F	-	-	-	-	•	-	-	-	F	F	•	G	**- 2nd**
TAF	•	•	-	G	-	-	-	•	•	F	G	-	-	-	-	-	•	•	•	G	•	•	-	**TAF**
TDF	-	•	-	-	-	-	•	-	-	-	-	-	-	-	-	•	-	-	-	-	•	•	-	**TDF**
- 2nd	-	•	F	G	G	G	G	-	-	F	G	-	•	-	-	•	-	-	•	-	•	•	G	**- 2nd**

2nd: Secondary patents relating to the previous ARV, including combinations (this entry may combine information on several patents); exceptions are TAF and TDF

*** :** expected to have expired around August 2013 in most jurisdictions

Diagonal shading: compulsory licence issued

Dark shading: countries/medicines covered by licences or technology transfer agreements with at least one company

Light shading: countries/medicines covered by licences or technology transfer agreements with at least one company limited to paediatric formulations

G: granted patent application**; F:** filed patent application; **-:** no patent granted/no patent application filed; **•:** status of patent application unknown

16 The information in the table should not be considered a complete and authoritative source of patent information on ARVs. The table provides a snapshot at a particular point in time (31 January 2014) and is based on the information that was available to the Medicines Patent Pool; it includes only some of the patents relating to each ARV.

Annex I. Summary table on ARV patents and licences (continued)[17]

	Kyrgyzstan	Malaysia	Mexico	Moldova	Mongolia	Montenegro	Morocco	Nicaragua	OAPI	Pakistan	Panama	Paraguay	Peru	Philippines	South Africa	Sri Lanka	Tajikistan	Thailand	Turkey	Ukraine	Uzbekistan	Venezuela	Viet Nam	
ABC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**ABC**
- 2nd	G	G	G	G	-	-	G	•/-	G	G	G	-	G	G	G	G	G	F	G	G	•	•	-	- 2nd
ATV	-	G	G	-	-	-	-	-	•	G	•	-	-	G	G	-	-	F	-	-	-	-	-	**ATV**
- 2nd	-	G	G	-	-	-	-	-	•	G	•	-	G	G	G	-	-	G	G	G	-	F	-	- 2nd
COBI	F	-	F	F	-	-	•	-	G	-	•	-	-	-	F	-	F	•	-	G	-	-	F	**COBI**
- 2nd	F	-	F	F	-	-	•	-	•	-	•	-	-	-	F	-	F	•	-	F	-	-	F	- 2nd
DRV	-	-	-	-	-	-	-	-	-	-	•	-	-	-	-	-	-	•	-	-	-	-	-	**DRV**
- 2nd	G	-	G	G	-	-	-	-	•	-	•	-	-	G	G	-	G	•	G	-	-	-	F	- 2nd
DTG	G	F	F	G	-	-	G	-	•	-	-	-	-	G	G	-	G	-	-	G	-	-	F	**DTG**
- 2nd	•	•	•	-	-	-	-	-	•	-	-	-	•	-	•	-	•	-	-	•	-	-	•	- 2nd
EFV *	-	-	G	-	-	-	-	-	-	-	•	-	-	-	G	-	-	G	-	G	-	-	-	**EFV ***
- 2nd	G	-	F	G	-	-	•	-	•	-	•	-	-	-	G	-	F?	F	G	-	-	F	-	- 2nd
ETV	G	G	G	G	-	-	•	-	G	F	•	-	-	G	G	G	G?	•	G	G	-	-	G	**ETV**
- 2nd	•	•	G	-	-	-	•	-	•	-	•	-	-	-	-	-	G	•	G	-	-	•	-	- 2nd
EVG	-	G	G	-	-	-	•	-	•	-	•	-	G	G	G	-	-	-	-	-	-	F	F	**EVG**
- 2nd	F	G	G	F	-	-	•	-	•	-	•	-	-	G	G	-	F?	F	-	-	-	F	F	- 2nd
LPV	-	-	G	-	-	-	-	-	-	-	•	-	-	G	G	-	-	G	-	-	-	-	-	**LPV**
- 2nd	G	•	G	G	-	G	-	•	•	F	•	-	G	G	G	G	G	F	G	G	-	-	G	- 2nd
MVC	G	G	G	G	-	G	G	-	G	-	G	F	G	G	G	F	G	•	G	G	G	-	G	**MVC**
- 2nd	G	-	G	G	G	G	G	-	G	-	G	-	G	G	G	-	G	F	G	G	G	-	F	- 2nd
NVP	-	-	-	-	-	-	-	-	G?	-	•	-	-	G?	G?	-	-	-	-	-	-	-	-	**NVP**
- 2nd	F	G	G	F	-	G	G	-	•	F	•	-	G	G	G	-	F?	F	G	G	G	F	G	- 2nd
RAL	-	-	G	-	-	G	•	-	•	-	•	-	-	G	G	-	-	-	G	G	G	-	G	**RAL**
- 2nd	-	G	G	-	G	-	G	F	•	F	•	-	-	G	G	-	-	F	G	G	-	-	F	- 2nd
RPV	•	F	G	•	-	-	•	•	G	F	G	-	-	F	G	G	G	-	G	G	-	F	F	**RPV**
- 2nd	G	•	G	G	•	-	•	•	•	•	•	-	•	F	G	-	G	•	G	G	•	-	F	- 2nd
RTV	-	-	G	-	-	-	-	-	-	-	•	-	-	G	-	-	-	-	-	-	-	-	-	**RTV**
- 2nd	G	G	G	G	-	G	•	-	-	-	•	-	-	G	G	G	G	F	G	G	-	•	G	- 2nd
TAF	-	-	F	-	•	•	-	•	F	•	•	•	-	-	G	•	-	•	-	G	•	•	F	**TAF**
TDF	-	-	-	-	-	-	-	-	-	-	•	-	-	-	-	-	-	-	-	-	-	-	-	**TDF**
- 2nd	G	•	G	G	•	-	•	•	•	•	•	-	-	F	G	•	G	F	G	G	•	F	G	- 2nd

2nd: Secondary patents relating to the previous ARV, including combinations (this entry may combine information on several patents); exceptions are TAF and TDF

***** : expected to have expired around August 2013 in most jurisdictions

Diagonal shading: compulsory licence issued

Dark shading: countries/medicines covered by licences or technology transfer agreements with at least one company

Light shading: countries/medicines covered by licences or technology transfer agreements with at least one company limited to paediatric formulations

G: granted patent application; **F:** filed patent application; **-:** no patent granted/no patent application filed; **•:** status of patent application unknown

17 The information in the table should not be considered a complete and authoritative source of patent information on ARVs. The table provides a snapshot at a particular point in time (31 January 2014) and is based on the information that was available to the Medicines Patent Pool; it includes only some of the patents relating to each ARV.

Annex II. Overview of patents and licences relating to selected fixed-dose combinations

Combination	Patents and patent applications	Existing voluntary licences	Developing countries where competition may potentially be delayed due to patents/patent applications/licences[18]
ABC/3TC	Secondary patents and patent applications on ABC and on ABC/3TC combination.	Licences available for 118 countries (paediatrics) and 69 countries (adult).	Paediatric formulations: Brazil, Belarus, China, Kazakhstan, Jordan, Mexico, Peru, Ukraine. Adult formulations: countries outside sub-Saharan Africa, low-income countries and least-developed countries.
ABC/3TC/DTG	Patents and patent applications on DTG granted or pending in several developing countries. Secondary patents on ABC and ABC/3TC granted in several jurisdictions.	Paediatrics licences available for 121 countries; adult licences available for sub-Saharan Africa, least-developed countries, low-income countries, Egypt, India, Indonesia, Philippines, Turkmenistan and Viet Nam.	Countries outside the licensed territories in which there are granted patents.
ATV/r	Patents on ATV pending in India and granted in a number of other countries. Patents on RTV and RTV tablet formulation also granted in several developing countries.	Four licenses for sub-Saharan Africa, and two for India. In December 2013, licence granted to the MPP covering 110 countries.	Countries outside the 110 countries covered by the licence with the MPP in which there are granted patents (China, Egypt, Indonesia, Malaysia, Mexico, Peru, Thailand and Ukraine) and countries in which there are patents on ritonavir.
DRV/r	Patents on RTV, RTV tablet formulations and secondary patents on DRV filed or granted in several developing countries.	Commitment not to enforce DRV patents in sub-Saharan Africa and least-developed countries and licence for India.	Albania, Armenia, Azerbaijan, Belarus, Bosnia, Brazil, China, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, South Africa, Sri Lanka, Tajikistan, Turkey, Turkmenistan, Ukraine and Viet Nam
LPV/r	Patents on LPV and on the LPV/r tablet formulation have been granted in several jurisdictions, but not in India (a key country of manufacture).	None.	Albania, Armenia, Argentina, Azerbaijan, Belarus, Bosnia, Brazil, Chile, China, Colombia, Dominican Republic, El Salvador, Georgia, Guatemala, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Montenegro, Pakistan, Peru, Philippines, South Africa, Sri Lanka, Tajikistan, Turkey, Ukraine and Viet Nam.
TDF/FTC/EFV **TDF/3TC/EFV**	There are patents or patent applications on TDF/FTC and TDF/FTC/EFV, which may not cover TDF/3TC or TDF/3TC/EFV, depending on the exact text of those patents or patent applications. TDF patents have been granted in China and Mexico, and EFV patents recently expired (except in Ukraine).	Licences on TDF/FTC cover 112 countries and were issued to many ARV manufacturers in India and South Africa.	For TDF/FTC/EFV: Argentina, Azerbaijan, Belarus, China, Mexico, Turkey, Ukraine and Venezuela.
TDF/FTC/EVG/COBI	Patents and patent applications on COBI, EVG and TDF/FTC in several developing countries.	Licences available to various manufacturers for up to 112 countries.	Countries outside the 100 countries included in the voluntary licences.
TDF/FTC/RPV	Patents on RPV, TDF/FTC and TDF/FTC/RPV in several developing countries.	Licences available to various manufacturers for 112 countries.	Countries outside the 112 countries included in the voluntary licences.

18 Preliminary analysis based on publicly available information on patents, patent applications, voluntary licences and compulsory licences and limited to the countries covered in this report (see Section 1.7). Given its preliminary nature, the information contained in the table should not be considered a complete and authoritative source of patent and licensing information on antiretrovirals. The table provides a snapshot at a particular point in time and is based on the information that was available to the Medicines Patent Pool and UNITAID; it includes only some of the patents relating to each antiretroviral combination.

Annex III. Licensing policies by ARV

For most licence agreements, only basic information is known, such as the name of the licensees, the geographical scope and, in some cases, the royalties payable to the licensors. Other terms and conditions are generally kept confidential,[19] thus preventing a detailed analysis. However, it is important to note that, in addition to the terms mentioned above, many other provisions may have an important impact on access, market competition and the development of adapted formulations, including fixed-dose combinations.

ARV	Number of licensees	Geographical scope	Comments
Abacavir	Several	Paediatrics: 118 Adults: 69	Paedatrics: licensed through the MPP (full text of licence on MPP website)
Atazanavir		110 countries	Licensed to the MPP in December 2013 and available for sub-licensing
	Four (Aspen, Emcure, Mylan and Ranbaxy)	Sub-Saharan Africa and India: 49 countries	In the form of immunity-from-suit agreements
	Farmanguinhos	Brazil	In the form of a technology transfer agreement
Cobicistat	Several (including Aurobindo, Emcure, Hetero, Laurus, Mylan, Ranbaxy, Shasun, Strides)	Non-exclusive: 103 countries Semi-exclusive: 9 countries	103 countries through the MPP (full text of licence on MPP website); 9 countries on semi-exclusive basis to one licensee
Darunavir	Unknown	Sub-Saharan Africa, India and least-developed countries	Commitment not to enforce
Dolutegravir	One and available for sub-licensing from the MPP	Paediatrics: 121 countries Adults: sub-Saharan Africa, least-developed countries, low-income countries, Egypt, India, Indonesia, Philippines, Turkmenistan and Viet Nam	Licensed to the MPP in April 2014
Efavirenz	Several (Emcure, Sonke, Aspen, Aurobindo, Cipla-Medpro and Adcock Ingram)	South Africa	-
Elvitegravir	Several (including Aurobindo, Emcure, Hetero, Laurus, Mylan, Ranbaxy, Shasun, Strides)	Non-exclusive: 100 countries Semi-exclusive: 9 countries	100 countries through the MPP (full text of licence on MPP website). Other countries on semi-exclusive basis
Etravirine	None	-	There are packaging and distribution agreements with at least one company
Lopinavir	None	-	-
Maraviroc	None	-	-
Raltegravir	Two (Emcure and Mylan)	Sub-Saharan Africa and low-income countries	
	One	Brazil	In the form of a technology transfer agreement
Rilpivirine	Five (Aspen, Emcure, Hetero, Mylan and Strides Arcolab)	112 countries	
Ritonavir	None	-	-
Tenofovir alafenamide fumarate	None (product still in phase III)	-	-
Tenofovir disproxil fumarate	Several	112 countries	Licensed through the MPP (full text of licence on MPP website)

19 The exception is the licences negotiated by the MPP.