Increasing access to HIV treatment in middle-income countries

Key data on prices, regulatory status, tariffs and the intellectual property situation

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Abbreviations

ARV	antiretroviral
BMS	Bristol-Myers Squibb
GNI	gross national income
GPRM	Global Price Reporting Mechanism
HS	Harmonized Commodity Description and Coding System
INN	international nonproprietary name
MPP	Medicines Patent Pool
OECS	Organization of Eastern Caribbean States
PCT	Patent Cooperation Treaty
PEPFAR	United States President's Emergency Plan for AIDS Relief
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
UNAIDS	Joint United Nations Programme on HIV/AIDS
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

HIV treatments

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/r	atazanavir with ritonavir
COBI	cobicistat
D4T	stavudine
DDI	didanosine
DRV	darunavir
EFV	efavirenz
ETV	etravirine
EVG	elvitegravir
FTC	emtricitabine
LPV	lopinavir
LPV/r	lopinavir with ritonavir
MVC	maraviroc
NVP	nevirapine
r	ritonavir
RAL	raltegravir
RPV	rilpivirine
SQV	saquinavir
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disproxil fumarate
TPV	tipranavir
ZDV	zidovudine

Executive summary

This paper was originally developed as a background paper for the Consultation on Access to HIV Medicines in Middle-Income Countries, which was held from 10 to 12 June 2013 in Brasília, Brazil. It focuses on the challenges middle-income countries are facing in accessing affordable HIV treatment. Middle-income countries include a wide array of countries ranging from US$ 1036 to US$ 12 615 GNI per capita.[1] For example, the 103 countries that World Bank currently rates as middle-income countries, include 17 least developed countries. This is due to the different selection criteria used. While the World Bank's main criterion for classifying economies is gross national income (GNI) per capita, the United Nations Committee for Development Policy uses three criteria for identifying countries as least developed countries: gross national income per capita, the human asset index and the economic vulnerability index. This results in a larger number of poor people (living on less than US$ 2 per day) living in middle-income countries than in low-income countries *(1)*. Due to the increase in national income it is expected that by 2020 the vast majority of people affected by HIV will be living in middle-income countries. International aid and assistance, however, still focuses on low-income countries.

The paper provides information on the prices paid by 20 middle-income countries for adult and paediatric formulations of antiretroviral (ARV) drugs recommended by the World Health Organization (WHO).[2] It links this information with an analysis of the intellectual property situation of the selected ARV medicines using the patent status database of the Medicines Patent Pool (MPP) *(2)*, and includes data and general information on a number of other determinants of prices and availability of ARVs, including tariffs, markups and taxes, as well as an overview of the regulatory status.

The data show that the middle-income countries are a heterogeneous group and that procurement prices vary widely. Middle-income countries supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, including India and middle-income countries in Africa, are paying low prices for first-line and many second-line treatment regimens, comparable to those paid by low-income countries. Some countries – mainly in eastern Europe (Kazakhstan, the Russian Federation and to a lesser extent Ukraine) – are paying very high prices for many ARV drugs. Middle-income countries in Latin America (Argentina, Brazil) and Asia (China, Thailand) do pay relatively high prices for a number of second-line and third-line treatments. With some exceptions, countries that are sourcing products from originator producers are likely to pay higher prices.

First-line treatment regimens. Countries that stand out as having paid more than US$ 300 per patient-year for at least one way of administering the WHO-recommended first-line treatment regimen include Brazil, China, Cuba, Ecuador, Kazakhstan, the Russian Federation, Thailand and Ukraine. Cuba, Thailand and Ukraine could have used an alternative way to administer this treatment, which would lead to lower procurement prices. For the Russian Federation, the 10% tariff line possibly contributes to this high price.

Second-line treatment regimens. Most countries were able to source a second-line regimen for less than US$ 500 per patient-year, except Brazil, China, Indonesia, Kazakhstan,

1 Low income, US$ 1035 or less; lower middle income, US$ 1036–4085; upper middle income, US$ 4086–12 615; and high income, US$ 12 616 or more.

2 It should be noted that in the meantime the World Bank classifies Chile and the Russian Federation as high-income economies.

the Russian Federation and Ukraine. The Russian Federation sourced lopinavir/ritonavir from the originator, which is a major cost driver. In all these countries, at least secondary patents on these products have been granted or applications are pending that may prevent the countries from purchasing generic versions.

Third-line drugs. All middle-income countries face the challenge of high to very high prices for third-line drugs. Even in Nigeria and South Africa, which can access third-line drugs at reduced prices from the originator companies, the cumulative price of darunavir, raltegravir and etravirine has been in excess of US$ 3000 per year. Patents relating to raltegravir and etravirine have been granted in China and India, two of the main sources for active pharmaceutical ingredients and generic products. Currently, there are no pre-qualified generic versions of raltegravir and etravirine available. This makes it impossible even for those countries where patents have not been granted to procure generic versions of these products. While in principle local production would be an option, the patents granted in China and India prevent the export of the respective active pharmaceutical ingredients. Setting up local production in countries where these drugs are not protected by patent would thus require local production of active pharmaceutical ingredients. Leaving aside questions of cost efficiency and quality standards, this is beyond the capacity of most manufacturers in these countries.

Paediatric formulations. As for adult formulations, countries of eastern Europe (Kazakhstan, Russian Federation and Ukraine) and China are paying the highest prices for paediatric formulations. They are sourcing their abacavir, zidovudine, lamivudine, nevirapine and lopinavir/ritonavir nearly exclusively from the originator companies, which may be due to the patent situation in these countries. In general, the price of paediatric treatment regimens, when available, is slightly higher than that of first-line adult formulations.

New ARVs and pipeline products. The prices of drugs that are in the development pipeline or which have recently received regulatory approval are not yet known. It will be important to secure access to any new drugs that offer new therapeutic perspectives and that might need to be introduced in ARV therapy programmes soon. This will probably include drugs such as cobicistat, dolutegravir, elvitegravir, tenofovir alafenamide fumarate and rilpivirine. Patents on all of these ARVs either have been granted (elvitegravir, rilpivirine and tenofovir alafenamide fumarate) or are pending (cobicistat and dolutegravir) in India, where the largest ARV manufacturers are based today, and have all been granted in China, which is another important manufacturer of active pharmaceutical ingredients *(2, 3)*.[3] This may have a significant impact on the competitive procurement of these new ARVs in the future, unless the patent holders will grant licences for their manufacture and sale. Currently, the patent holders of cobicistat, elvitegravir and rilpivirine have granted voluntary licenses for generic production and sale in 100 to 112 countries (the first two via the MPP). The MPP negotiates further agreements on dolutegravir, and tenofovir alafenamide fumarate (TAF). If concluded these agreements will facilitate procurement of cheaper generic versions by those countries that are included in the licenses, while middle-income countries outside these agreements will have to pursue other avenues to reduce costs. The MPP announced the conclusion of an agreement on dolutegravir on 1 April 2014 which has not been taken into account in this publication.

3 Detailed analysis of the patents relating to these ARV drugs can be found in the I-MAK roadmap *(3)*. For patent status information on these ARV drugs in developing countries, see the MPP patent status database *(2)*.

Regulatory status. In addition to price, slow regulatory approval was identified as an obstacle to access to ARVs. For example, out of the countries assessed, only 10 are on record as having registered the WHO-recommended three-drug fixed-dose combinations used in first-line treatment. Regulatory approvals for solid formulations for children are lagging behind. This limits the ability to provide patients with the best possible user-friendly treatment options, which is a known risk for non-adherence. This leads to less-than-achievable treatment outcomes and higher hospital and care costs to deal with complications, and might result in the emergence of drug resistance. An additional problem is that, when key formulations *are* registered, there is often only one supplier with regulatory approval. This limits the supply options and competition, with a potential negative impact on procurement prices.

Data exclusivity rules can delay the market entry of generic manufacturers, as they cannot register their products during the exclusivity period unless they replicate the clinical tests. The available data show that at least 9 out of the 20 middle-income countries have implemented data exclusivity in their national laws. Besides data exclusivity, the reason for lack of regulatory approval can be that manufacturers simply choose not to apply for regulatory approval for their products in a given market. In this case, consideration of the decisions of other (trusted) regulatory authorities or – where appropriate – WHO prequalification outcomes may facilitate the registration of generic versions. This could also lead to lower prices for current or future products.

Tariffs, markups and taxes. With respect to tariffs, the data show that in general tariffs are zero per cent or rather low, with a few exceptions. Overall, tariffs are not likely to be a major price driver. Controlling markups added along the supply chain is important and can contribute to cost savings, in particular for drugs distributed through the private sector. Where ARVs are provided through the public sector free of charge, markups play a limited role. Taxes can be a major cost driver for medicines in general, but this paper does not provide data enabling an assessment of their impact on access to ARV drugs. In general, countries should consider abolishing taxes on essential medicines and control markups. Detailed guidance is provided in the new *WHO guideline on country pharmaceutical pricing policies (4)*.

Patents, voluntary and compulsory licences. To assess the impact of patent protection on prices of and access to ARVs, one has to look at the patent status of each drug on a country-by-country basis, taking into account the current voluntary licence agreements as well as compulsory licences.

Voluntary licences are allowing those middle-income countries that are included in the geographical scope of these agreements to procure generic products from the licensees, but only certain middle-income countries are included in the scope of the agreements (for a detailed list of products and countries, see Table A3.1, Annex 3). Given that pharmaceutical companies consider many of these countries as markets, it is unlikely that all middle-income countries will be included in future agreements under the current conditions. Key questions in this regard are:

- What criteria should be used to determine a reasonable price for middle-income countries?
- How can the inclusion of more middle-income countries be facilitated?

Compulsory licences have been used by a number of countries to access cheaper ARV treatment, including Brazil and Thailand (for a list of all compulsory licences, see Table A3.2, Annex 3). The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, and the United Nations 2011 Political Declaration on HIV/AIDS, mention the flexibilities of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), which includes compulsory licences as one mechanism that can be used to increase access to essential medicines. The mere fact that a compulsory licence could be issued by a government also increases the bargaining power of governments in price negotiations. When used, compulsory licences allow for the import or local production of generic versions. Where there is no generic production (yet), as in the case of some of the third-line drugs, countries cannot import the products readily and the only option would be local production with all its caveats. Where local production is not possible, countries can revert to an additional flexibility adopted by WTO members in 2003. This mechanism allows the import of pharmaceutical products from a WTO member country that has granted a special compulsory licence exclusively for the export of these medicines. However, the use of this mechanism, often referred to as the Paragraph 6 System, has been limited and its impact remains to be evaluated.

Strict rules on patentability criteria, as introduced by some countries, can limit the number of secondary patents. For example, the absence of patents on fixed-dose combinations or paediatric versions allows earlier market entry of these products.

Conclusions

There is no one-size-fits-all solution for middle-income countries. The data show that prices for the same products vary widely from country to country. The situation varies from product to product, often depending on the patent landscape and the geographical scope of licence agreements, but there is a clear divide separating the middle-income countries paying very low or high prices for first- and second-line ARV drugs. Those countries that are paying high prices may take different measures to tackle this situation and increase value for money. This includes furthering registration of generic products where available, switching to cheaper combinations where possible, and monitoring the patent situation and applying strict patentability standards in line with obligations under the WTO TRIPS Agreement. Where patents are granted, voluntary licences and other arrangement can be a means to lower costs. Where negotiations with patent holders fail, compulsory licences are an option that a number of countries have used in the past. The data presented suggest that tariffs do not play a major role in most countries, but countries should control whether tariffs, taxes or markups are major cost drivers.

All low- and middle-income countries face the challenge of access to third-line and pipeline drugs. Treatment cohorts worldwide are ageing and demand for those drugs will probably become more urgent. These more recent products are more widely patented, including in the countries that are currently the main sources for affordable quality generics. To attain access to treatment for all, it is now important to focus on those drugs and explore options to facilitate access in all middle-income countries. One option is the MPP, which already signed agreements on cobicistat, elvitegravir and tenofovir disoproxil fumarate in 2011 and on abacavir paediatric and atazanavir in 2013. The MPP is currently negotiating licences on dolutegravir, tenofovir alafenamide fumarate (TAF) and paediatric lopinavir/ritonavir. It remains to be seen whether the MPP will be able to secure licensing agreements covering these and other products.

To further the ability of middle-income countries to access ARV drugs at a price they can afford, the countries that participated in the consultation considered increasing information exchange on their prices and their determinants. WHO already makes available databases on the price[4], the regulatory status[5] and the production capacity of active ingredients of ARV medicines. The MPP collects and disseminates information about patent status of HIV/AIDS medicines. It is critical that these instruments remain available and are expanded to address the information needs of middle-income countries. More transparency is a first step towards the definition of an individual price reduction strategy.

4 Global Price Reporting Mechanism for HIV, tuberculosis and malaria. WHO HIV/AIDS website: http://www.who.int/hiv/amds/gprm/en/index.html.

5 WHO drug regulatory status database: http://apps.who.int/hiv/amds/patents_registration/drs/.

1. Introduction

1.1 Purpose of paper

This paper focuses on the 20 middle-income countries that participated in the Consultation on Access to HIV Medicines in Middle-Income Countries, which was held from 10 to 12 June 2013 in Brasília, Brazil. . The data were completed after the consultation, based on further input received by countries, at which stage data from a few middle-income countries that did not participate in the consultation (Belarus, Guyana, Jamaica and Moldova) and from the pooled procurement operations by the Organization of Eastern Caribbean States (OECS) were added. Notwithstanding these additional data, information gaps remain.

The paper provides information on the prices paid by middle-income countries for adult and paediatric formulations of antiretroviral (ARV) drugs recommended by the World Health Organization (WHO).[6] It links this information with an analysis of the intellectual property situation of the selected ARV medicines using the patent status database of the Medicines Patent Pool (MPP) *(2)*, and includes data and general information on a number of other determinants of prices and availability of ARVs, including tariffs, markups and taxes, as well as an overview of the regulatory status. It aims to provide factual information to inform discussions and highlight areas where knowledge gaps exist, which if addressed would facilitate the identification of appropriate actions to increase access to ARV medicines. It does not address other important determinants of access, such as national procurement systems or political willingness to provide treatment at low prices to those who need it. The picture emerging from the available data does enable an assessment of the situation of access to ARVs in middle-income countries, at least at the national level, and identifies several actions that middle-income countries could pursue to improve it.

1.2 Sources of data

The source of the data presented in this section is the WHO Global Price Reporting Mechanism (GPRM).[7] The GPRM compiled the price and volumes of ARVs bought by low- and middle-income countries from international wholesale suppliers (such as the International Development Association, the United Nations Children's Fund, MissionPharma, the Supply Chain Management System and the Clinton Health Access Initiative), or recorded in the price and quality reporting of the Global Fund to Fight AIDS, Tuberculosis and Malaria, or paid for by the Government of the United States of America through the United States President's Emergency Plan for AIDS Relief (PEPFAR). These data are in the public domain, as the GPRM database is accessible and searchable on the World Wide Web. In addition, prices made available by the Ministries of Health of Brazil, China, Kazakhstan and South Africa, and prices obtained by the WHO country offices from official sources in the Russian Federation and Thailand, are included. The prices shown in this paper are the lowest prices paid by the countries for a given formulation in the period spanning 2010 to 2013, made available to WHO up to 15 May 2013. The prices shown are ex-works prices, and therefore do not include the cost of transport, insurance, taxes, duties and distribution margins.

6 It should be noted that in the meantime the World Bank classifies Chile and the Russian Federation as high-income economies.

7 Global Price Reporting Mechanism for HIV, tuberculosis and malaria. WHO HIV/AIDS website: http://www.who.int/hiv/amds/gprm/en/index.html.

Whenever possible, it is indicated whether the drugs were bought from the originator company or from a generic producer.

Finally, the convention used in this paper is to place the active ingredients used in tablets between square brackets. So [A + B] denotes a fixed-dose combination tablet of drug A and drug B, and [A] denotes a tablet containing drug A only. In adult formulations the strength of the tablets is omitted, but in paediatric formulations it is included.

The data on the regulatory status of ARVs presented here are sourced from the WHO drug regulatory status database.[8] This database contains information contributed on a regular basis by those producers of ARVs that have obtained prequalification through the WHO prequalification programme or approval from a drug regulatory authority member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. In addition, information on the regulatory status of domestically produced ARVs contributed by the Brazilian Ministry of Health is included. However, information on producers that held regulatory approval from other regulators or organizations was not available to WHO, and is therefore not presented. Finally, the information is accurate only to the extent that WHO has been provided with complete data.

The patent data stem from the MPP database *(2)*. The tariff data were contributed by the WTO Secretariat.

1.3 Treatment 2.0 initiative

In 2011, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO launched the Treatment 2.0 initiative *(5)*, which aims to optimize and increase access to treatment through the pursuit of efficiency gains. It has five pillars:

- optimize the drugs and regimens used
- support the use of point of care and simplified diagnostics
- support decentralization and service integration
- facilitate community support
- promote cost reduction for the commodities used.

In pursuit of aims of the Treatment 2.0 initiative, WHO has since, in 2013, launched a revision of its guidelines on the use of ARV therapy. The 2013 revision proposes further simplification of ARV treatment across treatment indications (such as treatment for one's own health and treatment to prevent transmission of HIV from mother to child prior to, during and after delivery) and between groups in need of treatment (e.g. adults and children, and people with and without concomitant tuberculosis) *(6)*.

8 WHO drug regulatory status database: http://apps.who.int/hiv/amds/patents_registration/drs/.

2. Price data for selected ARV treatments

2.1 Adult formulations

To retain focus on state-of-the-art treatment and in line with the guidance on ARV therapy proposed by WHO, this section focuses on those ARV treatment regimens that WHO recommends as preferred treatment options in its 2013 treatment guidelines (Box 2.1) *(6)*. In addition, drugs used in third-line treatment – raltegravir (RAL), darunavir (DRV), etravirine (ETV) and tipranavir (TPV) – are considered.

Box 2.1 WHO-recommended preferred treatment regimens for adults

First-line treatment regimen: tenofovir disproxil fumarate (TDF) + emtricitabine (FTC) or lamivudine (3TC) + efavirenz (EFV) once daily

Second-line treatment regimen: zidovudine (ZDV) + lamivudine (3TC) + lopinavir (LPV)/ritonavir (r) or atazanavir (ATV)/ritonavir

Except in the discussion on three-drug fixed-dose combinations used in first-line treatment, single-drug formulations of nevirapine (NVP) – which is becoming a less preferred non-nucleoside – are not considered. ARVs that are no longer recommended, such as stavudine, didanosine, or the older protease inhibitors saquinavir, indinavir, nelfinavir, and their different formulations, are not discussed in this paper.[9]

Prices paid for three-drug fixed-dose combinations used in first-line treatment

WHO advocates the use of three-drug fixed-dose combinations of ARVs in first-line treatment, which can be taken as *one pill once a day* (Box 2.2).

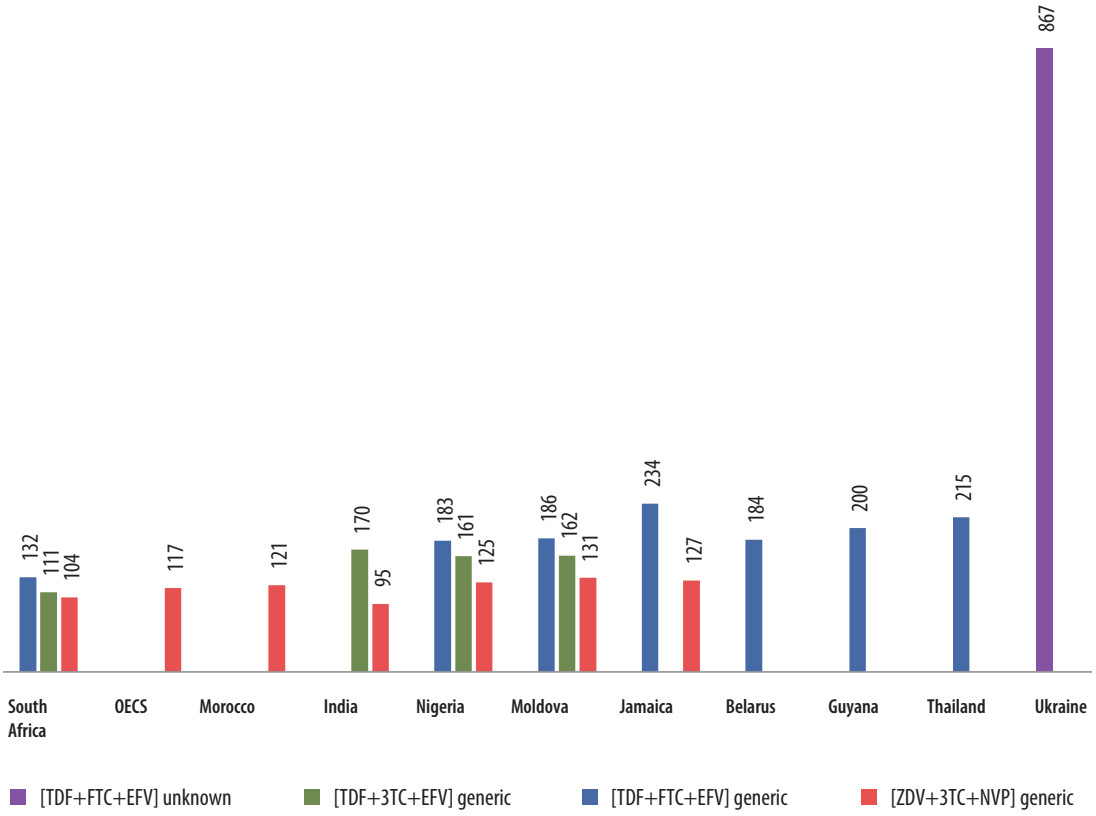
Box 2.2 Three-drug fixed-dose combinations

One pill once a day
combination of [TDF + FTC + EFV]
or
combination of [TDF + 3TC + EFV]
The less favoured alternative is to use the combination of [ZDV + 3TC + NVP], which needs to be taken *twice* a day.

Fig. 2.1 shows the prices paid for those combinations by different middle-income countries and by the OECS. Out of 24 middle-income countries and the OECS, 14 (Argentina, Brazil, Chile, China, Colombia, Cuba, Ecuador, Egypt, Guatemala, Indonesia, Kazakhstan, Mexico, Peru and the Russian Federation) are not on record as having procured any of the currently recommended three-drug fixed-dose combination products. While the procurement of ARVs by middle-income countries is likely to be underreported in the GPRM, and the procurement of three-drug fixed-dose combinations by some countries might not have been recorded here, it was confirmed that there is no access to those formulations in Brazil, China or the Russian Federation.

9 Information on their compulsory and voluntary licence agreements is however included in the section on intellectual property.

***Fig. 2.1** Prices (US$/patient-year) paid for currently recommended three-drug fixed-dose combinations*



In the 10 countries and the OECS, which are on record as procuring the currently recommended three-drug fixed-dose combinations, only one country – Ukraine – stands out as having paid a much higher price than others. However, Ukraine paid less for the same regimen by combining the two-drug fixed-dose combination of [TDF + FTC] with a single-product tablet of [EFV], and might have preferentially used the latter to secure affordable access to this treatment regimen. In other countries and the OECS, the price paid for different three-drug combination products was between US$ 95 to slightly more than US$ 230 per patient-year. [ZDV + 3TC + NVP] was slightly less expensive than other formulations in countries where its price could be compared to that of other formulations, and the prices reported for [TDF + 3TC + EFV] were slightly lower than those of [TDF + FTC + EFV].

All sales of triple-drug combinations reported were by generic suppliers, except Ukraine, where the identity of the supplier could not be confirmed. Thus, no inference can be made from these data on the relative efficiency of generic versus originator companies. In 2011 South Africa, which has a competitive market, bought [TDF + FTC + EFV] from the originator for between US$ 200 and US$ 212 per patient-year, and from generic sources for between US$ 197 and US$ 242 per patient-year. South Africa is however a rather particular market and an untypical middle-income country, in that (on average) it benefits from lower prices than other middle-income countries due to its geographical situation and the high burden of disease.

Prices paid for the WHO-preferred first-line treatment regimen

Box 2.3 shows the possible drug formulations for the WHO-preferred first-line treatment regimen.

Box 2.3 WHO-preferred first-line treatment regimen

The first-line treatment regimen TDF + FTC (or 3TC) + EFV can be administered as: a fixed-dose combination of all three drugs

or

a two-drug fixed-dose combination of [TDF + FTC (or 3TC)] with a tablet containing EFV only

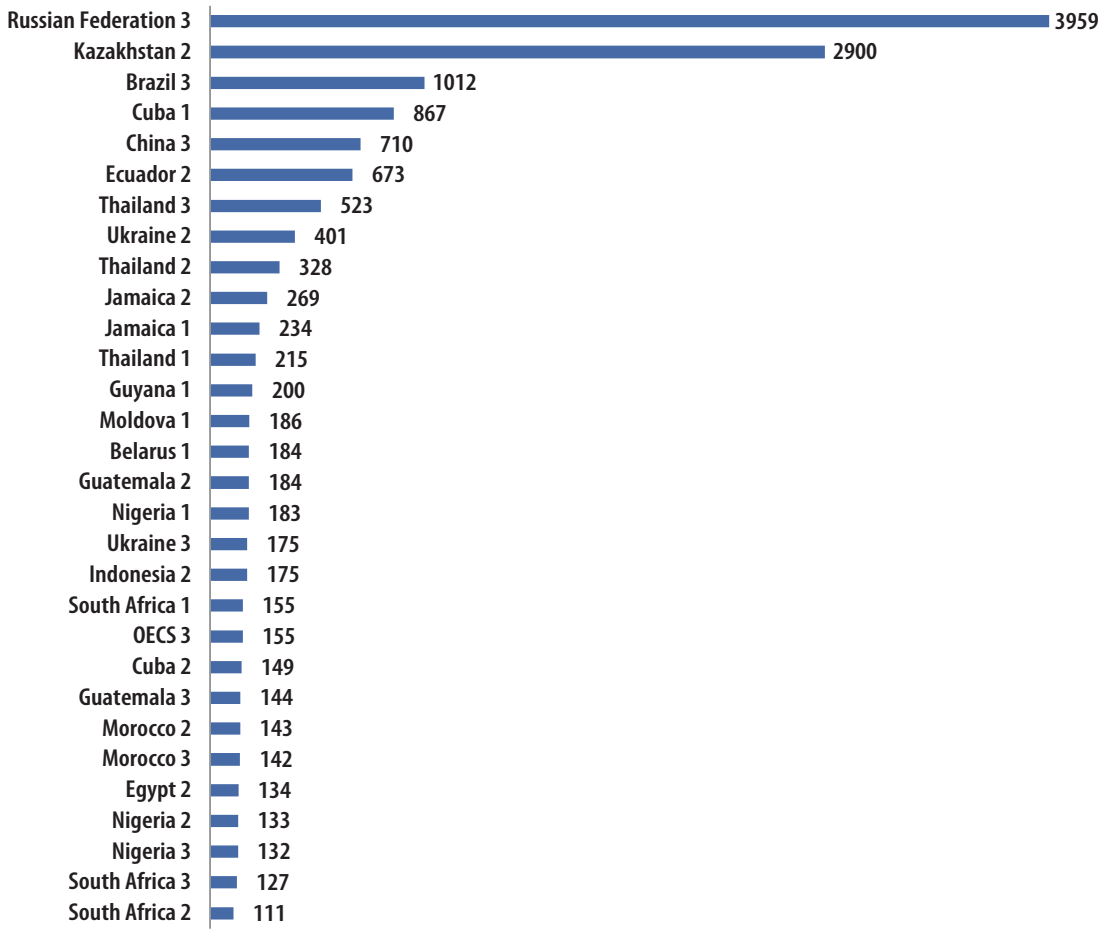
or

one tablet containing TDF only, one containing FTC or 3TC only, and one containing EFV only

Fig. 2.2 shows the prices that countries paid for each of these options. The number of daily tablets used in the regimen is mentioned after the name of the country:

- 1 for a regimen using one tablet a day (fixed-dose combination of all three drugs);
- 2 for a two-drug fixed-dose combination of [TDF + FTC (or 3TC)] with a tablet containing EFV only;
- 3 for a regimen requiring three or more tablets a day.

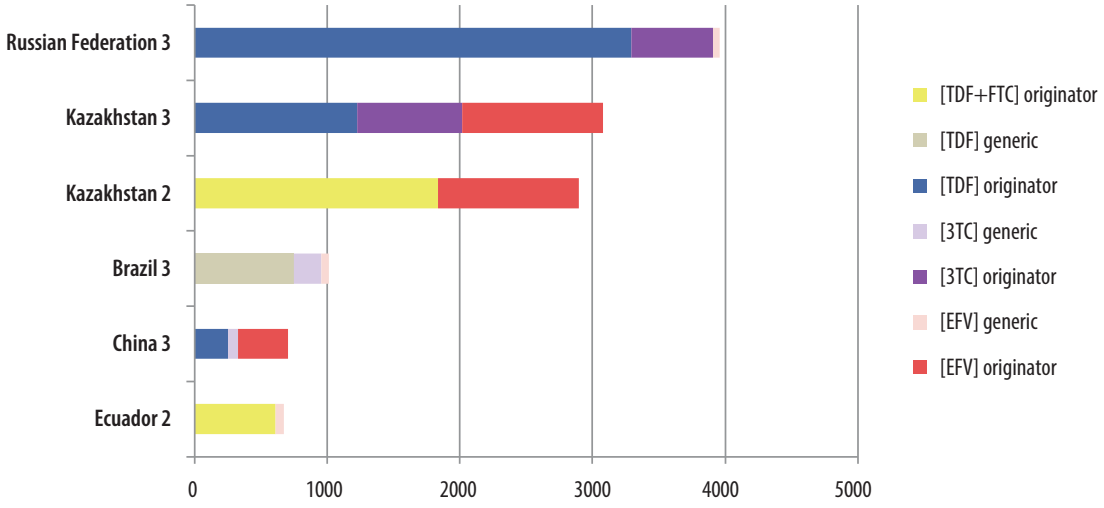
Fig. 2.2 Prices paid (US$/year) for WHO-preferred first-line regimen [TDF + FTC (or 3TC) + EFV]



Countries that stand out as having paid more than US$ 300 per patient-year for at least one way of administering this first-line treatment are Thailand, Ukraine, Ecuador, China, Cuba, Brazil, Kazakhstan and the Russian Federation. However, Thailand (by using a three-drug fixed-dose combination instead of a less preferred three daily tablets regimen), Cuba (by using two daily tablets instead of a three-drug fixed-dose combination) and Ukraine (when using three tablets instead of two tablets) could have used an alternative way to administer it, and would in that case have paid far less than US$ 300 per year. Therefore, only Ecuador, China, Brazil, Kazakhstan and the Russian Federation seem to have no alternative option.

Fig. 2.3 shows the price structure of their treatment regimens. The price of the regimen used in the Russian Federation is seen to be driven by [TDF] and [3TC], and in the case of Kazakhstan, by all three formulations used, which were sourced from the originator company. In principle both countries should be able to procure from generic sources as well, as no patent application on tenofovir fumarate salt was identified. The situation is different for the fixed-dose combination [TDF + FTC], for which a patent was granted in the Russian Federation, but apparently not in Kazakhstan. Patents on fixed-dose combinations have been granted or are pending in both countries (see Table A1.1, Annex 1, and MPP database).

***Fig. 2.3** Regimen composition and price paid for preferred regimen of [TDF + FTC (or 3TC) + EFV] in countries paying more than US$ 300 per patient-year for regimen*



Leaving the combination patents out, TDF is only patented in China, Indonesia and Mexico, where the application is still pending (see the MPP database). The Brazilian and the Indian patent offices rejected the patent application on tenofovir fumarate salt (WO9905150), opening the way for the production and procurement of generic versions. In the case of Brazil, the price is driven by [TDF] and [3TC], both from domestic generic producers. In China, most recently another patent on TDF was revoked (WO1998004569), but the patent on the TDF salt was granted, most likely preventing the procurement of generic TDF.

Indonesia issued a compulsory licence for TDF in 2013 allowing the local production or the import of generic TDF. Most of the middle-income countries thus in principle could procure generic TDF.

In the past this was complicated through the fact that Gilead's licence agreements allowed the licensees to sell the product in initially 95 countries, including Indonesia, Jamaica, Kazakhstan, Nigeria, South Africa and Thailand, but leaving out other middle-income countries. This situation has changed with the agreement signed by the MPP and Gilead in July 2011, which allows licensees to opt out of the TDF licence agreement and sell the product in all countries where the patents have not been granted. Gilead also expanded the geographical scope of its initial license agreements to 112 countries.[10]

Regarding EFV, three countries (Brazil, Indonesia and Thailand) have issued compulsory licences enabling them to procure generic EFV (see Table A3.2, Annex 3). In Brazil, the price of EFV did decrease from US$ 1.59 per dose for the originator product to US$ 0.43 per dose for the imported generic version of the drug following the issuance of a compulsory licence. While it remained lower than the price requested by the originator, by 2012 the price of domestically produced EFV 600 mg tablets increased to US$ 0.68 per tablet, or US$ 247 per treatment-year. At the same time other middle-income countries, such as Morocco or Ukraine, paid less than US$ 50 per treatment-year for the same drug sourced from Indian WHO-prequalified generic manufacturers. In other countries, no patent or patent application for EFV could be identified (Colombia, Guatemala, Peru – see Annex 1). The patent holder has granted a voluntary licence for South Africa to a number of generic producers (see Table A3.1, Annex 3) allowing for competition in the market. With the main patents expiring in 2013, generic versions of EFV should become more widely available in the future.

Prices paid for second-line treatment regimens

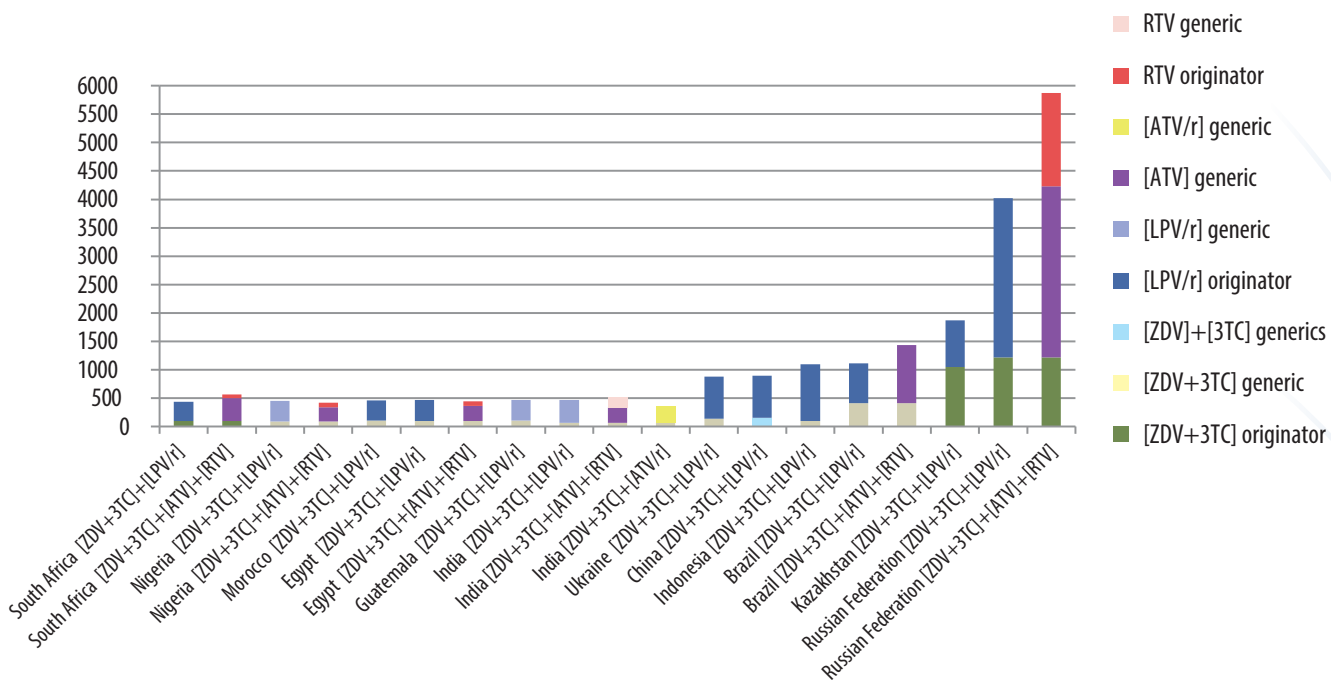
The second-line treatment recommended by WHO after failure of the WHO-preferred first-line regimen is zidovudine (ZDV) + lamivudine (3TC) + lopinavir with ritonavir [LPV/r], or atazanavir (ATV) + ritonavir (r). The last mentioned can be administered as a fixed-dose combination [ATV/r] or as tablets containing ATV only and ritonavir only (ATV + r). Fig. 2.4 shows how much middle-income countries paid for those second-line regimens.

With respect to ATV, Mylan, as well as a number of other generic companies, have signed immunity-from-suit agreements with Bristol-Myers Squibb (BMS) that allows them to sell ATV in sub-Saharan Africa and India, but not Latin America and other regions (see Table A3.1, Annex 3). Reportedly, middle-income countries outside sub-Saharan Africa and India have problems accessing generic ATV following a lawsuit for breach of this immunity-from-suit agreement by the patent holder BMS regarding sales by Mylan to Venezuela.[11] In light of these developments, some countries seem unable to buy generic ATV and its fixed-dose combination with ritonavir even if not patented in the respective jurisdiction. Instead they are using [LPV/r]. Patents on ritonavir also block the procurement of generic ATV/r in some countries (e.g. South Africa). The situation is likely to change with the signing of a licence agreement between BMS and the MPP that allows the latter to sublicense ATV to generic producers. The agreement covers 110 countries in total and, in addition, allows the sublicensees to market their products in all countries where no patents were granted,

10 See the list of countries included in the agreement: http://www.gilead.com/~/media/Files/pdfs/other/ExpandedTermsLicenseAgreement.pdf.

11 Text of the lawsuit: http://donttradeourlivesaway.files.wordpress.com/2012/08/b-m-s-complaint.pdf.

***Fig. 2.4** Prices (US$/patient-year) paid for second-line treatment [ZDV + 3TC] + [LPV/r] or [ATV/r] or [ATV] + [r]*



comprising another 34 countries.[12] This should allow 144 countries in total to procure ATV from generic companies that will sign sublicense agreements with the MPP.

This said, most countries were able to source a second-line regimen for less than US$ 500 per patient-year, except Brazil, China, Indonesia, Kazakhstan, the Russian Federation and Ukraine. In each of those countries, [LPV/r] sourced from the originator is a major cost driver. In all these countries, at least secondary patents on LPV and ritonavir were granted or applications are pending that may prevent them from purchasing generic versions. The originator company holding the patents on [LPV/r] currently does not have a voluntary licensing programme. Following Thailand and Ecuador, which issued compulsory licences in 2007 and 2010, respectively, Indonesia issued a compulsory licence in 2012 and will thus be able to procure generic [LPV/r].

In addition, in Kazakhstan and the Russian Federation, [ZDV + 3TC] sourced from the originator contributes to high costs. In Brazil, domestically produced [ZDV + 3TC] also contributes to the relatively high price. While less expensive than buying from the originator, domestically produced [ZDV + 3TC] is priced several times higher than in countries that source it from the international market.

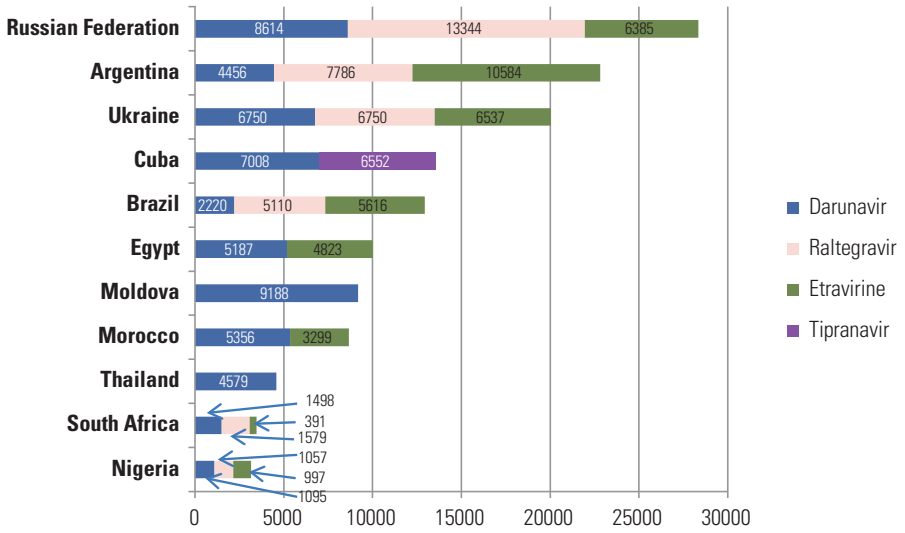
Prices paid for third-line drugs

WHO recommends that third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors, second-generation non-nucleosides, and protease inhibitors. However, WHO does not explicitly recommend a third-line regimen. Nevertheless, WHO suggests that darunavir (DRV) (with ritonavir boosting), raltegravir (RAL) and etravirine (ETV) be considered by countries in

12 See the text of the licence agreement, in particular 2.7(c) of the standard "Sublicense and technology transfer agreement": http://www.medicinespatentpool.org/licensing/current-licences/.

third-line regimens. In addition, some countries use tipranavir (TPV) in those regimens. Fig. 2.5 shows what the few middle-income countries that are on record as procuring third-line drugs have been paying for them recently. From this figure, it is clear that all countries have problems sourcing these third-line drugs at low prices. At current prices, middle-income countries could not afford to use any of those drugs as first-line treatment. Even in Nigeria and South Africa, which accessed the drugs at differential prices, the cumulative price of those three drugs has been in excess of US$ 3000.

***Fig. 2.5** Prices (US$/patient-year) paid for third-line drugs*



In addition to the novelty of these drugs and the fact that they are sole-source products available from the originator companies only, the small market for third-line drugs is also likely to contribute to higher prices in comparison to first- and second-line drugs, given the lack of economics of scale. According to reports from civil society organizations to the MPP, the number of people using third-line drugs in several middle-income countries is still very small: In 2012, in Brazil there were 5835 people on DRV, 6017 on RAL and 594 on ETV; in Russia, 9756 on DRV, 2644 on RAL and 2907 on ETV; in Argentina, 700 on DRV and 400 on RAL; and in Ukraine, 113 on DRV.

Despite the small numbers of patients receiving third-line treatment, countries providing third-line drugs are spending disproportionate amounts, given their high cost compared to first- and second-line drugs. For example, the International Treatment Preparedness Coalition in the Middle East and North Africa (ITPC-MENA) reported that in Morocco, where there are 5500 people on treatment, the amount spent on the procurement of third-line treatment for 20 people (at US$ 1700 per patient per month, or US$ 20 400 per patient per year) was equivalent to the amount required for treating 1700 people on first-line medicines (at US$ 240 per patient per year).

Patents relating to RAL and ETV have been granted in a number of countries, including two of the main sources of active pharmaceutical ingredients, China and India. Patents relating to DRV have been granted in a few countries, but not in Chile, Colombia, Guatemala, Peru, Thailand or Ukraine (see MPP database). With regards to DRV, the patent holder signed in 2008 a licence agreement with an Indian generic company, Emcure Pharmaceuticals

Limited, for the Indian market, although no patent seems to have been granted in India on DRV so far. Further details of the licence agreement have not been published. In 2012 the patent owner committed to allowing any generic company to sell generic DRV in sub-Saharan Africa and least developed countries (see Table A3.1, Annex 3). For DRV, Hetero is producing a generic version, which the Global Fund Expert Review Panel approved in May 2012 *(7)*.

For RAL, no patents could be identified in Guatemala, Kazakhstan or Peru. In principle, these countries should be able to procure from other sources than the originator, but currently there is no source for pre-qualified generic versions of RAL (and ETV). The originator company has signed licence agreements with two companies for RAL but they are limited to sub-Saharan Africa and low-income countries (see Table A3.1, Annex 3). So far, the licensees have not brought the product to the market.

In principle, local production in countries where the patents were not granted could be an option, but given the small local market in most countries economies of scale would be limited. In addition, to date annual surveys on production of active pharmaceutical ingredients for ARVs by WHO have been unable to identify suppliers offering the active pharmaceutical ingredients needed.

2.2 Prices for paediatric formulations

Similar to the discussion on the price of adult formulations, this section focuses on the price of paediatric formulations and regimens that WHO recommends as preferred treatment options (Box 2.4).

Box 2.4 WHO-recommended preferred treatment options for children

For children below 3 years:

abacavir (ABC) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r)

or

zidovudine (ZDV) + lamivudine (3TC) + lopinavir/ritonavir (LPV/r)

For children 3 years and above:

abacavir (ABC) + lamivudine (3TC) + efavirenz (EFV)

A widely used alternative regimen for both age groups is:

zidovudine (ZDV) + lamivudine (3TC) + nevirapine (NVP)

Preferably, those regimens are administered as solid formulations. The strength of the tablets and liquid formations is also included in the legend to figures, as in children formulations of a lesser strength than in adults are used. The prices of all treatment regimens presented here have been calculated for a child with a body weight of 10 kg, to enable comparison of the cost of different treatment regimens. The discussion on the prices of paediatric treatment is limited to first-line treatment, as second-line treatment in children is not yet well standardized.

Figs. 2.6 to 2.9 show the prices and composition of different paediatric regimens. When a country was on record as procuring different formulations with which it could have administered a given regimen, the composition and price of all ways that it could have used to administer the regimen is shown. From the figures, it is clear that in the recent past only a minority of countries are recorded as having bought all formulations needed to administer the WHO-recommended paediatric treatment regimens for children. Only 8 of the 24 countries plus the OECS included in this paper are on record as having bought all drugs needed to administer the preferred regimen for children below the age of 3, ABC + 3TC + LPV/r, and 13 for ZDV + 3TC + LPV/r. Seven countries were on record as having bought all drugs constituting the preferred regimen – ABC + 3TC + EFV – to treat children between the ages of 3 and 10 years. Twelve countries were on record as having bought all drugs to administer the alternative regimen ZDV + 3TC + NVP.

***Fig. 2.6** Price paid (US$/patient-year) for and regimen composition of paediatric ABC + 3TC + LPV/r*

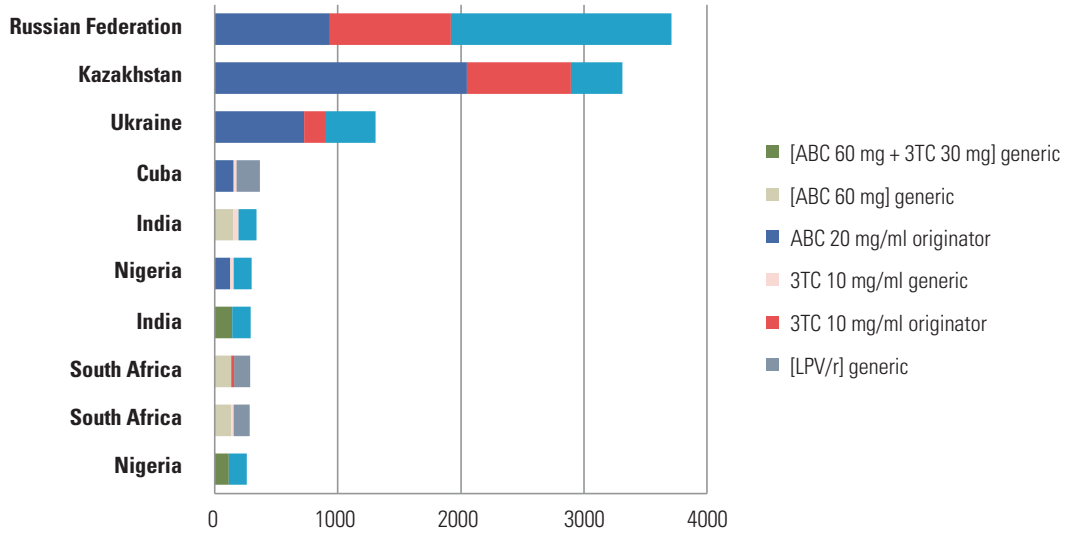


***Fig. 2.7** Price paid (US$/patient-year) for and regimen composition of paediatric ZDV + 3TC + LPV/r*

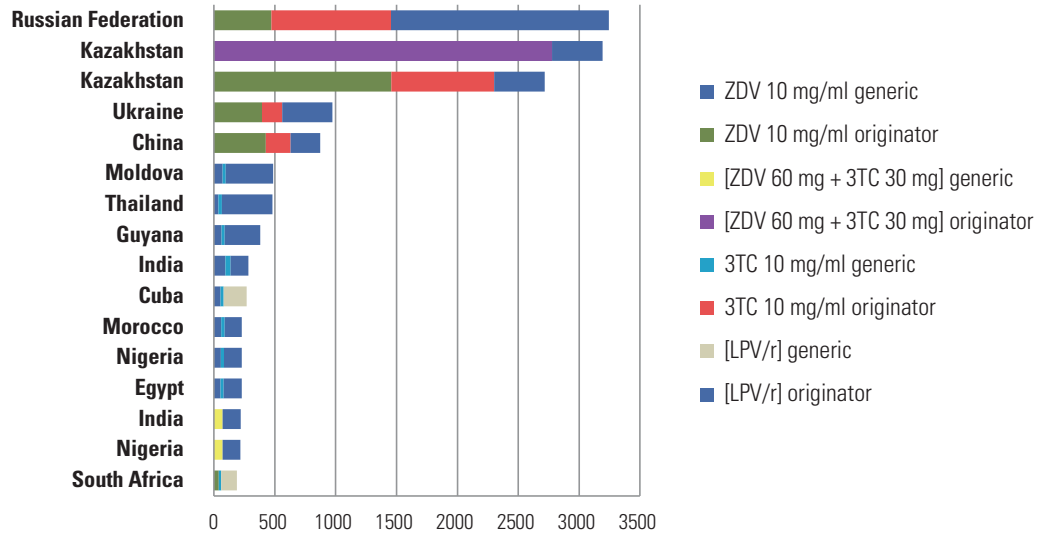


Fig. 2.8 Price (US$/patient-year) paid for and regimen composition of paediatric ABC + 3TC + EFV

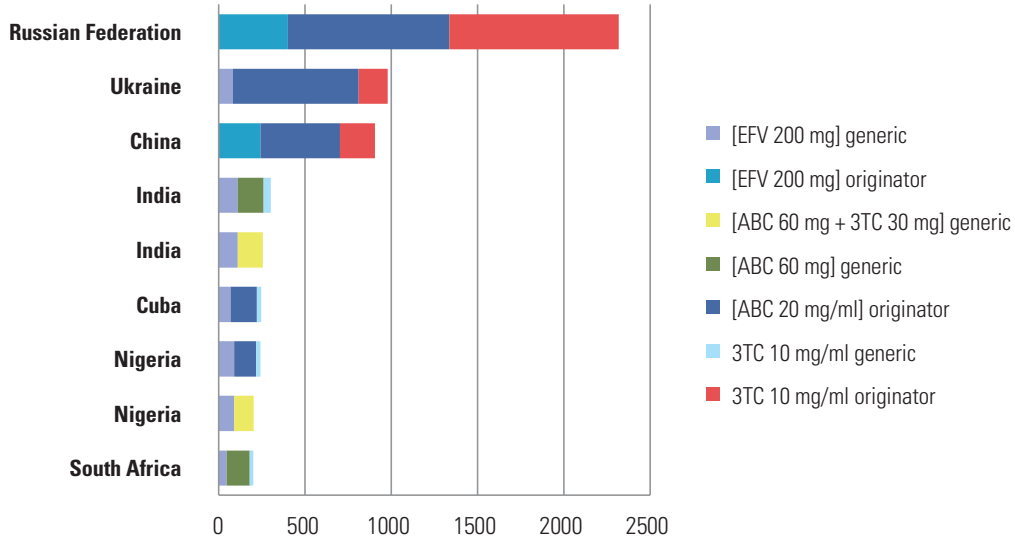
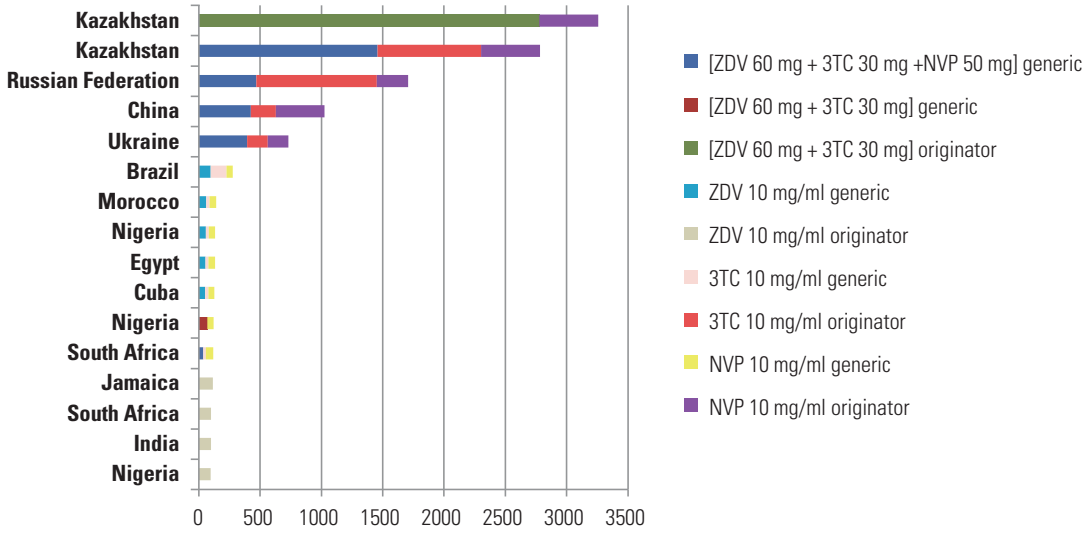


Fig. 2.9 Price paid (US$/patient-year) and regimen composition of paediatric ZDV + 3TC + NVP



As these regimens share to a great extent the use of key formulations, a common denominator emerges: Countries of eastern Europe (Kazakhstan, Russian Federation and Ukraine) and China are paying the highest prices. They are sourcing their ABC, ZDV, 3TC, NVP and LPV/r nearly exclusively from the originator companies. At least secondary patents on LPV/r and ABC have been granted in these countries. The highest price for LPV/r and EFV is paid by Russia. The relatively high tariff line for imported medicines of 10% may also contribute to this price.

Although paediatric formulations contain less active pharmaceutical ingredient than adult formulations, the price of paediatric treatment regimens, when available, is slightly higher than that of first-line adult formulations. The exception is the regimen ZDV + 3TC + NVP, of which the price matches the price of first-line adult treatment regimens (except in China, where the high price of ZDV and 3TC sourced from the originator company results in a much higher price than the adult regimen, for which the country uses generic versions of ZDV and 3TC). As the amount of active pharmaceutical ingredient in paediatric formulations is smaller than in adult formulations, the need to recover the development and marketing costs from a relatively small market and higher levels of profits are likely to explain this situation *(8)*.

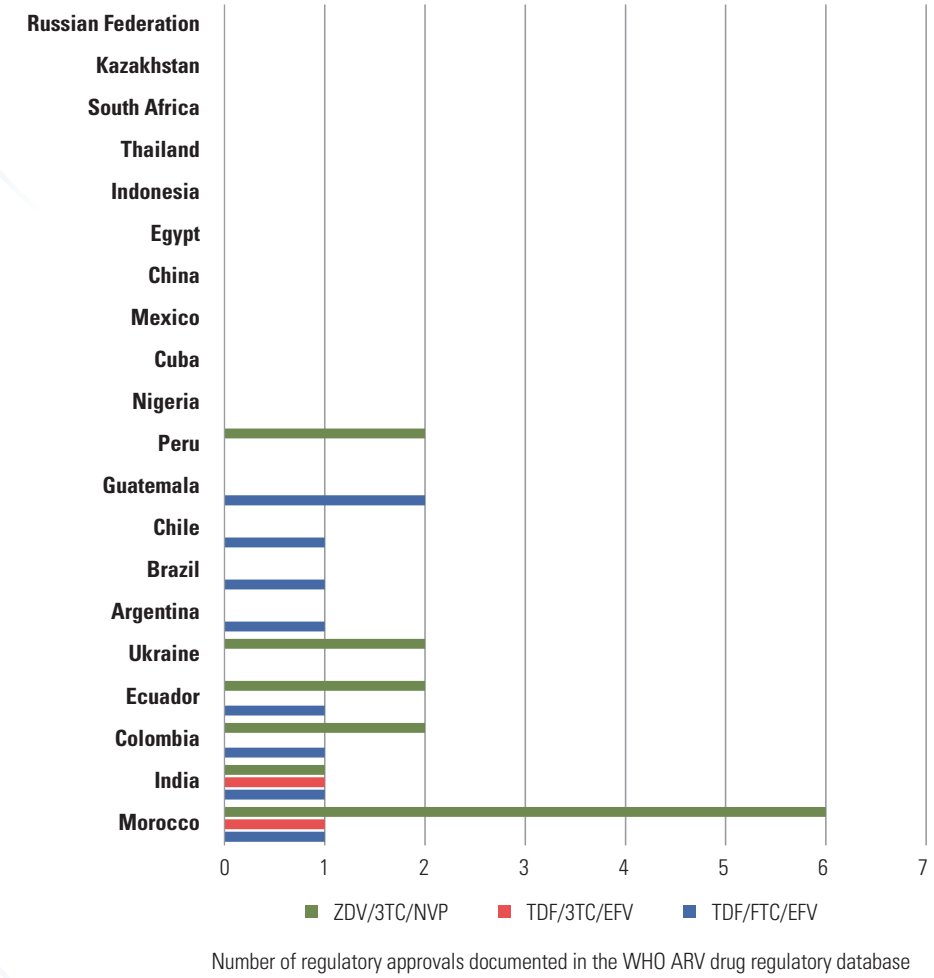
3. Regulatory status data for selected ARV treatments

3.1 Adult formulations

Regulatory status of three-drug fixed-dose combination products for first-line therapy

Fig. 3.1 shows the status of regulatory approval of three-drug fixed-dose combinations used in first-line treatment. For only 10 out of the 20 countries for which information was available, there is a record of regulatory approval of at least one three-drug fixed-dose combination. The lack of registration of these combinations is likely to be one factor explaining why the uptake of these easy-to-use formulations in middle-income countries is less than expected. Two countries (India and Morocco) have regulatory approvals for all three-drug fixed-dose combinations, a further two countries (Colombia and Ecuador) for two of those fixed-dose combinations, and six countries for only one fixed-dose combination. While the number of approvals in India is probably understated, as regulatory approvals are given at the level of states and might not have been reported at national level, very few countries are on record as having registered more than one manufacturer for three-drug fixed-dose combinations. This limits the number of supply options they can readily use and the leverage to increase the competitiveness of their market for those products. In five countries there was more than one manufacturer with regulatory approval for [ZDV + 3TC + NVP], and only one – Guatemala – had more than one supplier with regulatory approval for [TDF + FTC + EFV].

***Fig. 3.1** Regulatory status of three-drug fixed-dose combination products*



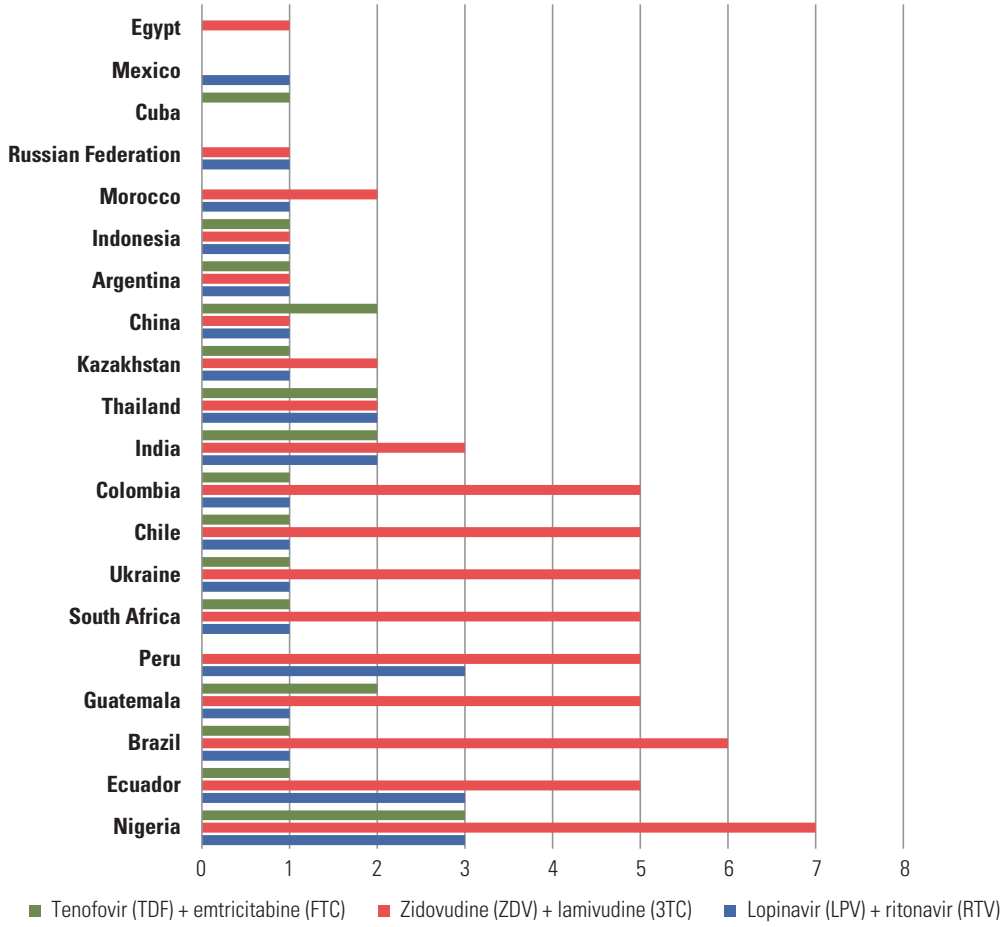
Number of regulatory approvals documented in the WHO ARV drug regulatory database

The regulatory landscape somehow is a reflection of the patent situation. Generic producers are unlikely to register their products in countries where legally they cannot market their products. However, the patent situation alone does not explain the limited number of regulatory approvals for three-drug fixed-dose combinations. Several other factors are likely to contribute to this situation, including the degree to which the producers are willing to invest time and effort in the regulatory process, the complexity of that process, and data exclusivity provisions in some of the countries (see Table 7.1).

Regulatory status of two-drug fixed-dose combination products

Fig. 3.2 shows the regulatory status of two-drug fixed-dose combinations. The majority of countries (15/20) have regulatory approval for all three fixed-dose combinations considered. Twelve out of 20 countries have regulatory approval for more than one supplier of [ZDV + 3TC], indicating that their market for this product is increasingly competitive. On the other hand, only five have regulatory approval for more than one producer of [LPV/r] or [TDF + FTC]. This limits market entry and competition for those products.

***Fig. 3.2** Regulatory status of two-drug fixed-dose combination products*



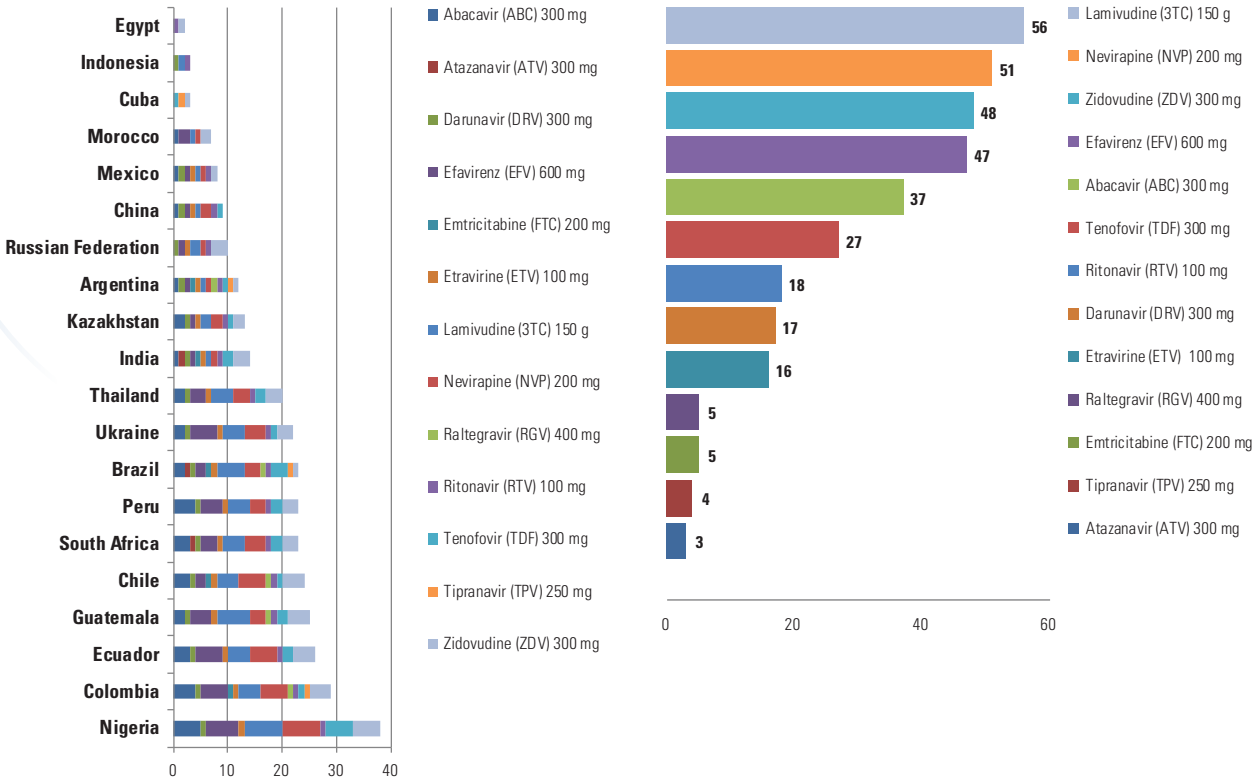
Regulatory status of single-drug formulations

The left-hand pane in Fig. 3.3 shows the number of regulatory approvals in place for 13 selected single-drug formulations for adults. The average number of regulatory approvals in place per country is 16.7, indicating that many countries have several companies with regulatory approval to supply the same formulations. On the other hand, at least 10 countries do not have regulatory

approval for one or more of the drugs listed. When there are less than five or six approvals in place, as would be the case in Egypt, Indonesia, Cuba and Morocco, it suggests that a proportion of the older ARVs (3TC, ZDV, NVP, EFV, ABC, tenofovir, and ritonavir) might still be used without regulatory approval. This could be due to the available data being incomplete – this is certainly the case for India, where generic medicines are regulated at state level. It could also be the case for Cuba, where limitations in trade have probably led to incomplete reporting by the suppliers. The other explanation could be that the formulations are used with a waiver of regulatory approval. While that is a possible measure to make needed drugs available, it also creates uncertainty among the suppliers about market entry. When systematically used, it also undermines the ability of the regulatory authority to guarantee the safety and quality of the medicines used in the country.

The right-hand side of Fig. 3.3 shows the number of regulatory approvals in place for different formulations in the same 20 countries. As expected, many countries have several regulatory approvals in place for the older drugs. However, the lack of regulatory approval is limiting access to third-line drugs, including FTC and ATV. Of note is that the latter drug appears to be used (as it was procured by their national programmes) by at least six countries, while it has regulatory approval in only three countries.

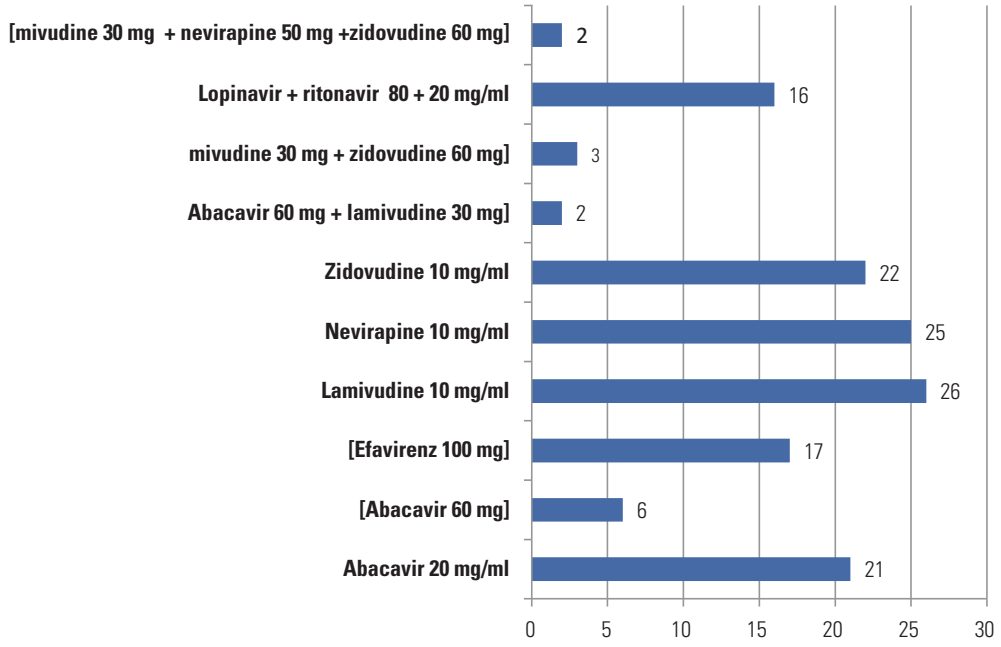
Fig. 3.3 Regulatory status of selected adult single-drug formulations



3.2 Regulatory status of paediatric formulations

Fig. 3.4 lists the number of regulatory approvals on record for selected paediatric formulations. With over 20 regulatory approvals in place in many countries, the older liquid paediatric formulations (of ABC, ZDV, 3TC and NVP) often have regulatory approval. However, the more recently introduced solid formulations (ABC, and combinations of ABC and ZDV with 3TC), which are important advances in paediatric treatment, are often not yet registered. EFV and LPV/r registration is progressing, but is also lagging behind.

***Fig. 3.4** Number of regulatory approvals for selected paediatric formulations in 20 countries*



Countries where selected paediatric formulations have more than one supplier with regulatory approval, and where consequently competition is possible, include Ukraine (six formulations), Chile (four formulations), Colombia (four formulations), Nigeria (four formulations), Peru (four formulations), Brazil (two formulations), India (two formulations – probably an underestimate), Thailand (two formulations) and Ecuador (one formulation). Countries with few (three or less out of 10) regulatory approvals on record for the selected formulations include Cuba, Egypt, Indonesia and Morocco.

4. Data on markups, taxes and tariffs

4.1 Impact of markups, taxes and tariffs on price

A markup represents the add-on charges and costs applied by different stakeholders in the supply chain to cover overhead costs and distribution charges, and to make a profit. The end price of a medicine thus includes markups that have been added along its supply chain. Markups can be added by all those who play a role in the supply chain, including wholesalers, retailers and pharmacists. Markups are common in medicine supply chain distributions in both the public and private sectors. For example, a secondary analysis of WHO/Health Action International surveys of developing countries indicates that wholesale markups ranged from 2% in one country to a combined markup by importers, distributors and wholesalers of 380% in another country *(9)*. Around 60% of low- and middle-income countries report regulating wholesale or retail markups *(10, 11)*. In the area of ARVs, markups are likely to play a less important role. This is due to the fact that ARVs are most often dispensed through the public sector or publicly funded and made available free of charge to the clients, which is not the case for many other medicines. In this case, markups over and above the ex-works price charged by the manufacturers are irrelevant to their end users. They can, however, impact the national health budget.

It is assumed that shipping, insurance, duty and delivery add on average 15% to the ex-works price of medicines when the medicines are sourced through international public tenders *(12)*. On the other hand, in less competitive national-level public procurement, importers and distributors have the ability to mark up their price. There is no comprehensive survey on markups in the area of ARVs. Therefore, it is impossible to assess to what extent markups contribute to the higher prices observed for ARVs in some countries.

Medicines are often also subject to indirect taxes such as purchase tax, sales tax or value added tax (VAT). Entities producing and selling medicines may also be subject to direct taxes on the revenue generated (e.g. corporate income tax). Taxes add to the end price paid by the consumer and are, therefore, a factor that affects access to medicines. Domestic taxes such as VAT or sales tax are often the third largest component in the final price of a medicine after the ex-works price and markups *(13)*. Of the participating countries, Colombia and Ukraine reported zero VAT and sales tax on medicines. In lower middle-income countries that charged taxes on medicines, the tax rate ranged from 5% to about 34% *(13)*. The data reported, however, were relatively old and would need to be updated to gain a more accurate picture on average rates of VAT and other taxes on medicines in middle-income countries. Thus, the assessment of the impact of taxes on ARV prices would require gathering up-to-date data on national VAT and sales tax. Detailed guidance is provided in the new *WHO guideline on country pharmaceutical pricing policies (4)*.

4.2 Tariff data on ARV drugs

Packaged medicines

The Harmonized Commodity Description and Coding System (HS) of tariff nomenclature is an international standard hierarchical coding structure used to classify traded products. The system consists of chapters, followed by headings and then subheadings. There is

no specific standard code at the most detailed classification of the HS (subheading level) for ARVs. HS chapter 30 covers pharmaceutical products. Within this chapter, ARVs are classified under subheading 3004.90, described as "medicaments consisting of mixed or unmixed products for therapeutic or prophylactic uses ...". Table A2.1, Annex 2, displays the tariff duties of selected middle-income countries for this subheading for the latest available year.[13]

The table provides the minimum, maximum and mean tariff duties for HS subheading 3004.90 applied in the countries with the data on actual applied tariff for ARVs, if available. In a few cases, countries have more detailed national tariff line breakdowns ("No. of tariff line" in Table A2.1) of their tariff schedule beyond the HS subheading level and with a national tariff line pertaining specifically to ARVs. Other countries impose a uniform tariff for all products within the subheading, making it relatively straightforward to identify the ARV tariff. Without an identifiable tariff line for ARVs, the subheading-level statistics are merely indicative of the possible actual tariffs for ARVs. To illustrate this, Egypt has its lowest tariff duty at 0% while the highest is at 5%, though it is not clear which of these tariffs applies to ARVs.

Of the 22 countries on display, there are seven where ARVs are imported duty free and five middle-income countries that have dutiable tariffs of 5% or lower. For four of the countries (China, Egypt, Jamaica and Mexico), the range of tariff duties is known, but the exact information regarding the actual duty for ARVs is not available. Nigeria has noticeably the highest tariff, at 20% for ARVs, with India and the Russian Federation both imposing a 10% tariff. No information is available for Kazakhstan.

Tariff data on bulk medicines and pharmaceutical goods

Bulk medicines are medicines that are not yet formulated (e.g. made into tablets) or packed for retail sale. Bulk medicines are usually imported with a view to carrying out certain segments of the manufacturing process domestically (e.g. formulation and packaging), depending on the form in which the medicines are imported. These tariff lines are thus more important for countries with some manufacturing capacity. In HS chapter 30, bulk medicines fall under two separate categories: heading 3003 relates to "medicaments consisting of two or more constituents which have been mixed together..." and heading 3006 relates to other "pharmaceutical goods …", which would include for example syringes of diagnostic kits. Tables A2.2 and A2.3, Annex 2, present the statistics at the heading level for these two headings and the actual ARV tariff, if identifiable.

Of the 21 countries in Tables A2.2 and A2.3, Annex 2, six have a 0% tariff when it comes to ARVs classified under HS heading 3003. For 10 countries, only the minimum and maximum range of tariffs is included, while the exact tariff applicable to ARVs is unknown. For HS heading 3006, only four middle-income countries have duty-free tariffs for ARV products. For other countries where the actual ARV tariff is not identifiable, the possible ARV tariff ranges from zero to 30%.

13 The tariff data referred to in this section and contained in Annex 2 were provided by WTO.

5. Role of patent and data protection for access to ARV treatment

This section provides a brief overview of the patent and data protection situation with regard to HIV/AIDS treatments. Due to the fact that HIV/AIDS is a relatively recent disease, many of the medicines that have been developed since the first appearance of HIV/AIDS are still under patent protection in certain countries. This is particularly the case for medicines used in second-line and third-line regimens and for the ARVs that have only recently received regulatory approval or are in late stage development.

Patents can be granted for products and processes if patentability criteria (such as novelty, inventive step or non-obviousness, industrial application or utility, and disclosure of the invention) are cumulatively met. Product patents in the area of medicines usually cover the chemical molecule or active ingredient (called base or primary patents in this document) or variations of an existing chemical molecule (called secondary patents in this document).

Examples of secondary patents include patents on fixed-dosed combinations (see for example the patents on rilpivirine in combination with TDF and FTC – *(2)*), new routes of delivery, new (dosage) forms (e.g. the patent on lopinavir soft gel capsules – *(2)*) or paediatric formulations (e.g. patent on composition of abacavir for paediatric use – *(2)*). The filing of patent applications on variations of the same medicine is a common practice and can delay the market entry of generic versions *(14)*. For example, while the base patent on abacavir expired in 2010, the patent on the hemisulfate salt will only expire in 2018, and the patents on the composition for paediatric use will only expire in 2019 (see MPP database).

Patents are territorial rights. The patent applicant may decide to apply for and pursue patent protection in one country or region but not in another. In practice, no patent application is filed in all countries, though using the World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT) allows filing one international patent application with effect in all PCT contracting States (148 contracting States by September 2013).[14] However, there is no international patent granted following the filing of international patent applications under the PCT system. National patents are granted separately in each country or region in which patent protection is sought, according to the applicable national or regional law and criteria. National and regional patent laws have different definitions and practices (e.g. for inventions relating to first or second medical use product patents, dosage regimes or variations of an existing chemical molecule). Section 3(d) of India's Patent Act and section 22 of the Philippines' Intellectual Property Code are two examples of a narrow definition of patentability criteria regarding variations of existing chemical compounds. Argentina adopted patent examination guidelines along similar lines to section 3(d) of India's Patent Act in May 2012 *(11)*.[15] Thus, a medicine can be patented in one country, but not in others. For example, the patent on tenofovir fumarate salt (WO9905150) was rejected in Brazil and India while it was granted in China and Mexico. Similarly, national patents can have different scope if claims are modified or restricted in the granting process.

14 WIPO PCT website: http://www.wipo.int/pct/en/pct_contracting_states.html.

15 Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute) of 5 May 2012, published in Official Gazette of 8 May 2012.

The question of whether a medicine is patented in the main ARV-producing countries is important. If a specific country does not have the ability to produce a medicine locally at the required quality and at competitive prices, the best option is to import the medicine. In cases, where the product is patented in the main producing countries, there may not be a source from where generic products can be imported. In this context, the patent situation in India is particularly relevant, as India is the main source of generic ARVs *(15)*. Annex 1, provides an overview of the patent situation of selected ARVs in middle-income countries based on the data contained in the ARV patent database of the MPP.

6. Role of voluntary licence agreements and compulsory licences

The owner of a patent can allow others to (also) use the invention and (for example) to manufacture, sell, export or import the patented product. Such permission is generally given in the form of a mutual agreement or voluntary licence. Further, under certain conditions, national authorities may allow government or third parties to use a patented invention without the authorization of the patent owner, often referred to as compulsory licences.

6.1 Voluntary licence agreements

Typical elements of a licence agreement are the scope of permitted use of a patented invention and the determination of royalties. Licences may be granted royalty free. Licences can be exclusive, allowing only the licensee to use the patented product; or non-exclusive, thus allowing licences to more than one company. A licence is generally provided for a defined number of countries (the defined territory) only. Besides the mere use of the patented invention, voluntary licences frequently include use of other intellectual property, such as know-how needed to use the invention or confidential test data.

Instead of licence agreements, some companies use so-called non-assert declarations or immunity-from-suit agreements. In such declarations or agreements, right holders state that they will not enforce (or not assert) patent rights against infringers under the conditions specified in the declaration or agreement and thus provide competitors, e.g. generic pharmaceutical companies, with legal room for action *(16)*. Non-assert declarations and immunity-from-suit agreements often contain an explicit set of conditions, including permitted actions and designated territories (i.e. a list of countries). For example, non-assert declarations of Boehringer-Ingelheim contain a condition that generic producers must be prequalified by WHO to ensure good quality, and allow generic manufacturers that fulfil that condition to market its HIV medicines in 78 countries, regardless of patent status in those countries *(17)*.

Table A3.1 (Annex 3) provides an overview of the known licence and immunity from-suit agreements and non-assert declarations.

In terms of geographical scope, most of the voluntary licences include countries in sub-Saharan Africa (including Nigeria and South Africa), as well as least developed countries and low-income countries. Middle-income countries that are not classified as least developed countries and are outside sub-Saharan Africa are not included in the scope of many of these agreements. The licences signed by the MPP with Gilead have the widest geographical scope for adult ARVs (between 100 and 112 countries accounting for all people living with HIV in low-income countries and 75–82% of those living in middle-income countries). Subsequently, Tibotec/Janssen signed agreements for RPV with the same geographical scope. Of the countries in this analysis, Indonesia, Jamaica, Kazakhstan, Nigeria, South Africa and Thailand are included in the list of 112 countries. The licence between the MPP and Viiv Healthcare on paediatric abacavir includes 118 countries (accounting for 98.7% of children living with HIV needing treatment), including 16 of those analysed in this document. The United Nations 2011 Political Declaration on HIV/AIDS encourages the use of licence agreements through patent pools to reduce treatment costs *(18)*.

In general, voluntary licence agreements result in segmenting the market: while the patent holder keeps the low-volume, high-profit markets in developed countries and emerging economies, the high-volume, low-profit markets are shared with generic competitors. In the case of markets for ARVs, this translates into, mostly, the markets of sub-Saharan Africa, least developed countries and low-income countries with, generally, a high disease burden of HIV/AIDS being shared with generic companies while originator companies focus on high- and many middle-income countries. While this addresses the needs of the weakest economies, it does not allow many middle-income countries to benefit from competitive procurement for certain ARVs, having to rely on a single supplier. Where to draw the line in this market segmentation will be answered differently from a business and a public health perspective. Key questions in this regard are:

- What criteria should be used to determine a reasonable price for middle-income countries?
- How can the inclusion of more middle-income countries be facilitated?

Given the fact that, with the notable exception of the agreements signed by the MPP, licence agreements are not made public, it is difficult to assess their content, including with respect to know-how and technology transfer, technical assistance or restrictive conditions for the licensees. In this respect, greater transparency regarding the main terms of these licences would be desirable. Both licensors and licensees also might need more guidance on how to maximize access through these agreements.[16]

6.2 Compulsory licences and government use declarations

In the absence of a voluntary licence agreement, one option to address public health needs under the current international legal framework is compulsory licences. A compulsory licence or a government use authorization issued by the competent national authority allows the licensee to use the subject matter of a patent without the authorization of the right holder. Government use occurs when the patent is exploited by the government or the government designates a third party to exploit the patent on the government's behalf without the authorization of the patent holder. However, often "compulsory licence" is used as the overarching term. Article 31 of the TRIPS Agreement contains certain conditions for both instruments. For example, except in cases of a national emergency, public non-commercial use or when remedying a practice adjudicated to be anticompetitive, Article 31 requires that the one who seeks a compulsory licence must first try to obtain a voluntary licence.[17] In this context, country experience has shown that the mere threat of compulsory licences can increase the bargaining power of governments in price negotiations.[18] Under a compulsory licence, countries can choose whether they want to import or locally produce the medicine. In this context, local production can be challenging, as it requires appropriate knowledge, technical capacity and access to a reliable source of active ingredients. Brazil, for example, reported that it took two years to locally produce EFV following the issuance of the compulsory licence.[19] In other cases, local production under compulsory licence may not prove to be sustainable, due in part to the limited local market. The export of medicines produced under compulsory licences is restricted by Article 31 of the TRIPS Agreement

16 For an analysis of access-maximizing terms and conditions, see Park et al. *(19)*.

17 See WHO, WIPO and WTO *(11)* pages 174–180 for further details.

18 WHO, WIPO and WTO *(11)*, page 177.

19 WTO *(20)*, paragraph 19.

requiring that any use of the patent without the authorization of the patent owner, which includes compulsory licences and government use, shall be "predominantly for the supply of the domestic market".

Table A3.2 (Annex 3) contains cases of compulsory licences pertaining to ARVs. As can be seen from the list in the table, compulsory licences have been used to increase access to medicines by enabling manufacturing or importing of lower-priced generic versions of HIV/AIDS medicines. For example, in Brazil the price for EFV reportedly dropped from US$ 1.59 per dose for the originator product to US$ 0.43 per dose for the imported generic version of the drug following the issuance of a compulsory licence.[20] With respect to the Thai government use declarations for EFV and LPV/r, a study estimated that they resulted in an additional 17 959 and 3421 patients having access to these treatments respectively *(22)*.

20 WTO *(21)*, paragraph 151.

7. Test data protection

Another form of intellectual property protection that can have an impact on generic competition is the protection of clinical test data that applicants for market authorization have to submit to national or regional regulatory authorities to prove the safety and efficacy of their products. Members of the WTO are obliged to protect such data against unfair commercial use and disclosure (Article 39.3 of the TRIPS Agreement). The underlying reason is the considerable investment in time and financial resources required to produce the data.[21] There are different ways in which this provision of the TRIPS Agreement has been implemented. Some countries protect clinical test data against disclosure, but do rely on them for regulatory approval of bioequivalent generic products. Other countries provide for data exclusivity over a certain period during which generic competitors cannot rely on clinical test data submitted by originator companies. Countries can have legal obligations to provide for a certain period of data exclusivity stemming from bilateral or regional trade agreements or accession agreements to the WTO.[22] In this context the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property[23] recommends that governments should take into account the impact on public health when considering adopting or implementing more extensive intellectual property protection than is required by the WTO TRIPS Agreement.

The way in which test data are protected can have an impact on the entry of generic products. At the outset, patent protection and test data protection are distinct issues and do not depend on each other. In a country where a specific medicine is patented, the period of data exclusivity may run in parallel with the patent term. In this situation data exclusivity has limited impact on generic market entry. This is different in countries where patent protection has not been sought, or where a patent was sought but not granted or was revoked, or where a patent has expired. In such cases, data exclusivity can delay the generic entry, as generic companies are unlikely to reproduce all the necessary data to prove safety and efficacy. On the other hand, the period of market exclusivity may provide an economic incentive to test the efficacy of medicines or to develop further such medicines, e.g. paediatric formulations, which may not be patentable in certain jurisdictions *(23)*. Table 7.1 provides an overview of whether the countries covered in this document provide for data exclusivity, indicating the length of the exclusivity period, where appropriate. According to the data available, 9 out of the 20 countries included in this study have implemented data exclusivity in their national laws. All 9 have international obligations stemming from either regional or bilateral free trade or WTO accession agreements. To what extent data exclusivity in the middle-income countries that have implemented this concept delays the market entry of specific products would require a country-by-country and product-by-product analysis. A number of studies have been undertaken that have identified data exclusivity as one of the elements in free trade agreements that has a considerable impact on medicine prices.[24]

21 For further information see WHO, WIPO and WTO *(11)*, pages 63–66.

22 For further information see WHO, WIPO and WTO *(11)*, pages 188–189.

23 Resolutions of the World Health Assembly 61.21 and 62.16.

24 See the studies referenced in WHO, WIPO and WTO *(11)*, page 190.

Table 7.1 Data exclusivity provisions

Country	Form of protection of undisclosed information			Agreements with data exclusivity obligations
	Exclusivity	Duration (from date of marketing approval in the country)	Extensions possible?	
Argentina	No	–	–	–
Brazil	No	–	–	–
Chile	Yes	5 years (from date of marketing anywhere in the world)	No	FTA with EFTA FTA with USA
China	Yes	6 years	No	WTO accession
Colombia	Yes	5 years	No	FTA with EFTA
Cuba	No	–	–	–
Ecuador	No	–	–	–
Egypt	No	–	No	–
Guatemala	Yes	5 years	No	CAFTA
India	No	–	–	–
Indonesia	No	–	–	–
Jamaica	Information not available			
Kazakhstan	Information not available			
Mexico	Yes	5 years	No	NAFTA
Morocco	Yes	5 years	3 years	FTA with EFTA FTA with USA
Nigeria	No	–	–	–
Peru	Yes	5 years	No	FTA with EFTA FTA with USA
Russia	Yes	6 years	No	WTO accession
South Africa	No	–	–	–
Thailand	No	–	–	–
Ukraine	Yes	5 years	1 year	WTO accession

FTA: free trade agreement

EFTA: European Free Trade Association

CAFTA: Central America Free Trade Agreement

NAFTA: North American Free Trade Agreement

Source: The table was developed based inter alia on IFPMA *(24)*; WHO pharmaceutical country profiles *(25)*; WHO, WIPO and WTO *(11)*, pages 186–190.

Annex 1. Overview of patent and licensing status per ARV

Table A1.1, on the patent and licensing status of selected ARVs, has been adapted from a patent landscape being prepared by the Medicines Patent Pool (MPP) and UNITAID. It is based on information contained in the MPP patent status database on ARVs and the information on current licences contained in Beyer 2013 (*16*) and in press releases of pharmaceutical companies.

The data contained in the MPP database was obtained from the national patent offices that made this information available directly to the MPP, via the World Intellectual Property Organization (WIPO) or in their respective online databases. For each ARV, the database contains a select number of patents. It should be noted that the list of patents may not be comprehensive and there may be other relevant patents for specific ARVs that are not included. Further, while the database is regularly updated, there may be a time lag between changes in the patent status of individual patents and the update of the database. Therefore, for the most up-to-date information on the patent status of a specific ARV it is advisable to consult the national patent office in the country of interest directly.

With respect to voluntary licences, the table indicates whether a given country has been included in the geographical scope of voluntary licences issued by the patent holder for a given product. As explained above, for several ARVs voluntary licences have been issued by the patent holders to one or more generic ARV manufacturers with different geographical scopes. It is important to note that in some cases voluntary licences may include countries where there are no patents or patent applications relating to a given product. This is because many countries import ARVs from other countries (e.g. India) where the product may be patented. In such cases, the inclusion of those countries where there is no patent enables licensees to manufacture the product in a country where the product is patented and export it to countries in which it is not.

Table A1.1 Summary table on ARV patents and licences

	AR**	BR**	CL**	CN**	CO**	CU**	EC**	EG**	GT**	IN**	ID**	JM**	KZ**	MX**	MO**	NG**	PE**	RU**	TH**	UA**	ZA**
ABC	-	-	-	-	-	-	•	-	-	-	-	•	-	-	-	•	-	-	-	-	-
- 2nd	G	F	G	G	G	-	•	G	G	G	G	•	G	G	G	•	G	G	F	G	G
ATV	G	G	G	G	-	-	•	•	-	F	-	•	-	G	-	•	-	G	F	-	G
- 2nd	G	-	G	G	-	-	•	F	-	-	G	•	-	G	•	•	G	G	F	G	G
COBI	F	F	-	F	-	-	•	•	-	F	F	•	F	F	•	•	-	F	•	G	F
- 2nd	F	•	-	F	-	-	•	•	-	F	F	•	F	F	•	•	-	F	•	F	F
DRV	-	-	-	-	-	-	•	•	-	-	-	•	-	-	-	•	-	G	•	-	-
- 2nd	F	F	-	G	-	-	•	•	-	-	F	•	G	G	•	•	-	G	•	-	G
DTG	-	F	-	F	G	-	•	F	•	F	G	•	G	F	G	•	-	G	-	G	G
- 2nd	-	•	-	F	-	-	•	-	•	F	F	•	-	•	-	•	•	F	•	-	•
EFV*	G	G	G	G	-	-	•	•	-	-	G	•	-	G	-	•	-	G	G	G	G
- 2nd	F	F	-	F	-	-	•	•	-	F	-	•	F	F	•	•	-	F	F	-	G
ETV	G	F	G	G	-	-	•	•	-	G	F	•	G	G	•	•	-	G	•	G	G
- 2nd	-	F	-	F	-	-	•	•	-	F	•	•	G	G	•	•	-	G	•	-	-
EVG	F	F	G	G	G	-	•	•	-	G	F	•	-	G	•	•	G	G	•	-	G
- 2nd	F	F	G	G	G	-	•	•	-	F	•	•	-	G	•	•	-	G	F	-	G
LPV	G	-	-	G	G	-	•	•	-	-	•	•	-	G	-	•	-	-	G	-	G
- 2nd	G	G	F	G	-	-	•	•	G	F	F	•	G	G	-	•	G	G	F	G	G
MVC	G	-	G	-	-	G	•	G	G	G	F	•	G	G	G	•	G	G	-	G	G
- 2nd	G	F	G	G	G	G	•	G	G	G	•	•	G	G	G	•	G	G	F	G	G
NVP	-	-	-	-	-	-	•	•	-	-	-	•	-	-	•	•	-	-	-	-	-

	AR**	BR**	CL**	CN**	CO**	CU**	EC**	EG**	GT**	IN**	ID**	JM**	KZ**	MX**	MO**	NG**	PE**	RU**	TH**	UA**	ZA**
-2nd	F	-	G	G	F	-	•	F	-	F	F	•	F	G	G	•	G	G	F	G	G
RAL	-	F	G	G	G	-	•	•	-	G	•	•	-	G	•	•	-	-	-	G	G
- 2nd	F	F	F	G	G	-	•	•	-	F	•	•	-	G	G	•	-	G	F	G	G
RPV	G	F	G	G	-	-	•	F	-	G	?	•	G	G	•	•	-	G	-	G	G
- 2nd	-	F	-	F	-	-	•	•	•	F	•	•	G	G	•	•	•	G	•	G	G
r	-	-	-	-	-	-	•	•	-	-	•	•	-	G	-	•	-	-	-	-	-
- 2nd	G	F	F	F	-	-	•	•	-	-	F	•	G	G	-	•	-	G	F	G	G
TAF	-	F	-	G	-	-	•	•	•	G	•	•	-	F	-	•	-	G	•	G	G
TDF	-	-	-	-	-	-	•	•	-	-	•	•	-	-	-	•	-	-	-	-	-
- 2nd	F	F	-	G	-	-	•	•	-	-	F	•	G	G	•	•	-	G	F	G	G

G : Granted
F : Filed/pending
- : Patent rejected, expired, lapsed, withdrawn or no patent or patent application identified
• : Status unknown
2nd: Secondary patents relating to the previous ARV, including combinations
* : expected to expire around August 2013 in most jurisdictions
** : AR-Argentina; BR-Brazil; CL-Chile, CN-China; CO-Colombia; CU-Cuba; EC-Ecuador; EG-Egypt; GT-Guatemala; IN-India; ID-Indonesia; JM-Jamaica; KZ-Kazakhstan; MX-Mexico; MO-Morocco; NG-Nigeria; PE-Peru; RU-Russian Federation.; TH-Thailand; UA-Ukraine; ZA-South Africa.

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

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

Blue shading: compulsory licence issued

No patent status information currently available for Ecuador and Nigeria.

Annex 2. Statistics on most favoured nation (MFN) tariff rates

Table A2.1 Statistics on MFN tariff rates for HS subheading 3004.90 for selected middle-income countries

Note: Subheading 3004.90 covers "medicaments consisting of mixed or unmixed products for therapeutic or prophylactic uses put up in measured doses or in forms or packings for retail sale…." For some countries the exact tariff line for ARVs could not be identified.

Country	Year	No. of tariff line	Applied tariff rate (%)			
			Mean	Min	Max	ARV
Argentina*	2011	63	10.4	0	14	0
Brazil*	2012	64	10.5	0	14	0
Chile	2012	2	6	6	6	6
China	2010	11	3.6	3	6	–
Colombia*	2012	7	7.9	5	10	5
Cuba	2012	1	1	1	1	1
Ecuador*	2011	7	5.7	5	10	5
Guatemala	2011	9	5	5	5	5
India	2012	70	10	10	10	10
Indonesia*	2012	19	4.7	0	5	0
Jamaica	2011	22	10.7	0	15	–
Kazakhstan	no data	–	–	–	–	–
Malaysia	2012	15	0	0	0	0
Mexico	2012	51	4.4	0	15	–
Morocco*	2011	14	3	2.5	10	2.5
Nigeria	2011	1	20	20	20	20
Peru	2011	7	6	6	6	6
Russian Fed.	2011	10	10	10	10	10
South Africa	2012	1	0	0	0	0
Thailand*	2011	16	8	0	10	0
Ukraine	2012	6	0	0	0	0
Egypt	2012	3	3.3	0	5	–

* The following countries have used national tariff lines beyond HS subheading 3004.90 specifically for ARVs. The following is a list of the specific national HS codes that they have individually used, in order of their appearance in the table above:

Argentina: HS 30049068 and HS 30049078
Brazil: HS 30049068 and HS 30049078
Colombia: HS 3004902400
Ecuador: HS 3004902400
Indonesia: HS 3004901000
Morocco: HS 3004907000
Thailand: HS 30049010, suffix 02

Source: WTO database.

Table A2.2 Statistics on MFN tariff rates for HS subheading 3003 (bulk medicines) for selected middle-income countries

Country	Year	No. of tariff line	Applied tariff rate (%)			
			Mean	Min	Max	ARV
Argentina*	2011	151	9.0	0	14	0
Brazil*	2012	151	9.0	0	14	0
Chile	2012	20	6	6	6	6
China	2010	30	5.8	5	6	–
Colombia	2012	10	5	5	5	5
Cuba	2012	7	1	1	1	1
Ecuador	2011	10	3.6	0	5	–
Guatemala	2011	25	2.3	0	5	–
India	2012	22	10	10	10	10
Indonesia	2012	14	4.4	0	5	–
Jamaica	2011	46	8.6	0	15	–
Malaysia	2012	31	0	0	0	0
Mexico	2012	43	7.3	0	15	–
Morocco	2011	29	16.5	2.5	30	–
Nigeria	2011	8	8.3	0	20	–
Peru	2011	10	6	6	6	6
Russian Fed.	2011	18	0	0	0	0
South Africa	2012	10	0	0	0	0
Thailand	2011	15	8	0	10	–
Ukraine	2012	12	0	0	0	0
Egypt	2012	11	1.8	0	2	–

* The following countries have used national tariff lines beyond HS heading 3003 specifically for ARVs. The specific national HS codes that they have individually used are as follows:

Argentina: HS 30039078 and HS 30039088

Brazil: HS 30039078 and HS 30039088

***Table A2.3** Statistics on MFN tariff rates for HS subheading 3006 (other pharmaceutical goods) for selected middle-income countries*

Country	Year	No. of tariff line	Applied tariff rate (%)			
			Mean	Min	Max	ARV
Argentina	2011	29	7.0	2	18	–
Brazil	2012	29	6.4	0	18	–
Chile	2012	13	6	6	6	6
China	2010	13	4.4	0	10	–
Colombia	2012	19	6.4	5	15	–
Cuba	2012	24	4.4	0	15	–
Ecuador	2011	19	5.4	0	15	–
Guatemala	2011	13	2	0	15	–
India	2012	16	7.5	0	10	–
Indonesia	2012	19	2.5	0	15	–
Jamaica	2011	11	0	0	0	0
Malaysia	2012	16	0	0	0	0
Mexico	2012	28	7.9	0	15	–
Morocco	2011	171	10.8	2.5	30	–
Nigeria	2011	11	2.2	0	20	–
Peru	2011	19	6	6	6	6
Russian Fed.	2011	18	8.5	0	15	–
South Africa	2012	11	0	0	0	0
Thailand	2011	19	9.6	0	30	–
Ukraine	2012	18	0	0	0	0
Egypt	2012	19	3.8	0	5	–

Source: WTO database.

Annex 3. Information on licences and agreements

Table A3.1 provides an overview of the known voluntary licences (VL), immunity-from-suit agreements (IFS), and non-assert declarations. Table A3.2 contains cases of compulsory licences for ARVs.

***Table A3.1:** Licences, immunity-from-suit agreements, and non-assert declarations for antiretrovirals*

INN	Licensor	Type	Earliest year	Geographical scope	No. of countries	Number of licensees	Royalty %
3TC	ViiV Healthcare[a]	VL	2010	LDC; LIC; SSA	69	Several	0
ABC (paediatric)	ViiV Healthcare through MPP[b]	VL	2013	Country list	118	MPP	0
ATV	BMS	IFS/VL	2006	SSA; India; Brazil[c]	49	Several	NA
ATV	BMS through MPP[b]	VL	2013	Country list	110	Several	3%
COBI	Gilead Sciences through MPP[b]	VL	2011	Country list	103	Several	5%
COBI	Gilead Sciences	VL	2011	Country list	103[f]	3	5%
d4T	BMS	IFS	2001	SSA; India; Country list	50	Several	NA
DDL	BMS	IFS	2006	SSA; India; Country list	50	Several	NA
DRV	Tibotec Pharmaceuticals (Janssen/J&J)	Non-assert/ VL	2012	Non-assert: LDC; SSA VL: India	65	1[d]	NA
EFV	MSD	VL	2007	South Africa[g]	1	Several	0
EVG QUAD TDF+FTC+EVG	Gilead Sciences through MPP[b]	VL	2011	Country list	100	Several	5%
EVG QUAD TDF+FTC+EVG	Gilead Sciences	VL	2011	Country list	100[f]	4	5%

INN	Licensor	Type	Earliest year	Geographical scope	No. of countries	Number of licensees	Royalty %
FTC	Gilead Sciences through MPP[b]	Non-assert	2011	Country list	112	Several	NA
NVP	Boehringer-Ingelheim GmbH	Non-assert[e]	2004/2007	LIC; LDC; Africa; India	78	Several	NA
RAL	MSD	VL	2011	LIC; SSA	56	2	0
RPV RPV/TDF/3TC or FTC	Tibotec Pharmaceuticals (Janssen/J&J)	VL	2011	Country list	112	5	2–5%
SQV	F. Hoffmann - La Roche Ltd	VL	2006	LDC; SSA	65	Several	0
TDF	Gilead Sciences	VL	2006	Country list	112	Several	5%
TDF	Gilead Sciences through MPP[b]	VL	2011	Country list	112	Several	3%[e]
TPV	Boehringer-Ingelheim GmbH	Non-assert[e]	2004/2007	LIC; LDC; Africa, India	78	Several	NA
ZDV ZDV/3TC	ViiV Healthcare[a]	VL	2001	LDC; LIC; SSA	69	Several	0

Explanations:

Licences can be exclusive, allowing only the licensee to use the patented product; or non-exclusive, thus allowing licencing to more than one company. A licence is generally provided for a defined number of countries (the defined territory) only. Instead of licence agreements, some companies use non-assert declarations or immunity-from-suit agreements. In such declarations or agreements, right holders state that they will not enforce (or not assert) patent rights against infringers under the conditions specified in the declaration or agreement.

"Several" in the column "Number of licensees" means more than five licensees.

"Country list" in the column "Geographical scope" indicates that there is a specific list of countries that have been included in the scope of the licence.

NA: not applicable

VL: voluntary licence

IFS: immunity-from-suit agreement

LDC: least developed country

LIC: low-income country

SSA: sub-Saharan Africa

QUAD: TDF/COBI/EVG/FTC

Notes:

a ViiV is an independent company combining HIV portfolios from GSK, Pfizer and Shionogi.

b Licences administered by MPP are publicly available on its website.

c Licence agreement with Farmanguinhos, Brazil, for Brazil only.

d Tibotec/Janssen also has distribution agreements with Aspen Pharmacare in South Africa for DRV and ETV under their brand names.

e Originally Boehringer-Ingelheim issued a voluntary licence in 2004, which was replaced with a non-assert in 2007. Covers public and private sectors. Companies may request a royalty-free licence for manufacturing in WHO prequalified plants.

f In addition, semi-exclusive licences with 10–15% royalties:
Mylan: Sri Lanka, Thailand
Ranbaxy: Botswana, Namibia
Strides Arcolab: Ecuador, El Salvador, Indonesia, Kazakhstan, Turkmenistan.

g No patents in Sub-Saharan Africa outside South Africa

Source: This information is based on Beyer (16), Park C et al. (19) and other publicly available sources, including the websites of the licensors.

Table A3.2 Compulsory licences for ARV drugs

Year	Issuing jurisdiction	Type	Income group	Sourcing	Royalty %	INN(s)
2003	Malaysia	GU	UMIC	Import	4%	DDI; ZDV; ZDV/3TC
2003	Zimbabwe	CL	LIC	Import/Local production	NA	HIV-related medicines
2004	Mozambique	CL	LIC	Local production	2%	3TC + d4T + NVP
2004	Zambia	CL	LMIC	Local production	2.5% max	3TC + d4T + NVP
2004	Indonesia	GU	LMIC	Local production	0.5%	3TC; NVP
2005	Ghana	GU	LMIC	Import	NA	HIV-related medicines
2006	Thailand	GU	UMIC	Import/Local production	0.5%	EFV
2007	Thailand	GU	UMIC	Import/Local production	0.5%	LPV/r
2007	Indonesia	GU	LMIC	Mainly local production	0.5%	EFV
2007	Brazil	GU	UMIC	Import/Local Production	1.5%	EFV
2007	Canada	CL[a]	HIC	Export[a]	2%	3TC + ZDV + NVP
2010	Ecuador	GU	UMIC	Import	0.42% of US price	RTV
2012	Indonesia	GU	LMIC	Local production	0.5%	ABC; DDL; EFV; LPV/r; TDF; TDF + FTC; TDF + FTC + EFV
2012	Ecuador	GU	UMIC	Local production	5% of US price[b]	ABC/3TC

Explanations:

NA: not available
CL: compulsory licence
GU: government use
LIC: low-income country
LMIC: lower middle-income country
UMIC: upper middle-income country
HIC: high-income country

Notes:

a Issued under so-called WTO paragraph 6 system for export to Rwanda.
b 5% of United States price adjusted by difference in GDP.

Source: The information was compiled from primary data sources (text of compulsory licences, issuing country communications, etc.) and Knowledge Ecology International *(26)*.

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