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ACCESS TO ANTIRETROVIRAL DRUGS IN LOW- AND MIDDLE-INCOME COUNTRIES

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

At the end of 2013, more than 11.7 million people were on antiretroviral therapy (ART) in low- and middle-income countries (LMICs). The 2013 World Health Organization (WHO) antiretroviral (ARV) guidelines are designed to extend these benefits more widely and will increase the potential number of people eligible for antiretroviral therapy (ART) to an estimated 28.6 million. However, whether ART can be expanded to cover their treatment needs depends on the extent to which the right ARVs are available and affordable.

In the past decade the price of individual ARV formulations has decreased considerably. Rather than continuing to use the least expensive ARVs, treatment programmes in LMICs have used this as an opportunity to replace stavudine (d4T)-based treatment with new and improved first-line medicines. The cost of first-line ARVs in LMICs has remained fairly constant. The WHO collates information on the cost of ARVs in the Global Price Reporting Mechanism (GPRM) on public procurement of ARVs in collaboration with GFATM, PEPFAR and international procurement organizations. In the GPRM database, which covers around 75% of all ARV use in LMICs, but which has limitations in recording procurement by upper middle income countries, the median annual cost of first-line ART varied from US$ 117 in 2011 to US$ 115 per patient per year (ppy) in 2013. The price of second-line and third-line ART documented in GPRM also decreased, but less so than first-line treatment. LMICs which can access generic drugs for second-line treatment paid approximately US$ 330 ppy in 2013. However, there are MICs that pay higher prices – typically Brazil, and Eastern European countries such as Kazakhstan, the Russian Federation and Ukraine. Higher prices have also been documented in other Latin American and Asian countries. The inability of these countries to access cheaper generic ARVs is a key factor explaining their higher prices. Finally, although the price of third-line treatment has decreased for low-income countries (LIC), they still pay more than US$ 1500 ppy for a combination of raltegravir (RAL), etravirine (ETV) and darunavir (DRV), and middle-income countries (MICs) pay considerably higher prices.

Since 2001, as new clinical evidence and drug formulations have emerged, five sets of new clinical guidelines for treatment of HIV/AIDS have been issued by WHO. They have had a direct effect on the use of key ARVs in LMICs. Positive developments include the increased use of tenofovir (TDF) and efavirenz (EFV) in first-line treatment. At the end of 2012, almost half of all people using ART in LMICs had TDF in their treatment regimen, and 50% used EFV. The uptake of second-line and third-line treatment regimens in LMICs remains low despite guidelines changes, with likely factors for this limited uptake in LMICs being the inability to diagnose treatment failure. Of concern, however, is the development and delivery of ARV formulations tailored for children, which still lags behind that of adults. The uptake of LPV/r, now recommended by WHO as the drug of choice in children aged less than three years, is low: it was limited to less than 3% of children in 2013. Limited diagnostic capacity is the most likely explanation for its low uptake. WHO and its IATT partners recently published a list of optimal paediatric ARV formulations to reduce market fragmentation and streamline procurement for paediatric ARV medicines. In addition, DNDi and Cipla Ltd are working on the development of new more user-friendly LPV/r formulations with support from UNITAID. Other formulations are urgently needed (ie. ATV/RTV, DRV/RTV, TDF/XTC/EFV) and some are currently under consideration (ie. ABC/3TC/EFV) by the Paediatric ARV Working Group.

The WHO's Prequalification of Medicines Programme (PQP), and the United States Food and Drug Administration (US FDA) approval process (tentative when there is still patent or exclusivity market protection for the product in the United States of America) continue to provide up-front quality guarantees for the ARVs that the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) and the United States President's Emergency Plan for AIDS Relief (PEPFAR) make available. WHO's PQP and the US FDA were pivotal in opening up the market to generic suppliers and competition, which was a critical factor enabling the decreasing prices of ARVs seen in the last decade. In addition, they enabled the introduction of several important formulations, which presently are not available in countries in which part or all of their content is protected by patents. However, only relying on WHO's PQP and the US FDA to secure access to high-quality ARVs is not a sustainable solution. For sustainable access to high-quality ARVs, countries should urgently strengthen the capacity of their national medicines regulatory authorities. In order to facilitate the rapid introduction of new ARV formulations into their markets, it is important that their national drug registration processes be simplified.

A number of important ARVs are still under patent protection. This limits the availability of cheaper generic versions in the countries concerned. Voluntary licences, in particular through the Medicines Patent Pool (MPP), are enhancing access to newer patented ARVs in a large number of LMICs. The main challenges now are in upper middle-income countries (UMICs) – countries that still pay high prices to access third-line medicines and new ARV products. For some of these products, licence agreements have been negotiated. While the geographical scope has expanded during the past few years, particularly for licences negotiated by the MPP, many of the UMICs are not included in these agreements. However, in the recent agreement on dolutegravir (DTG), the MPP for the first time used public–private market segmentation and different levels of royalties to reflect different income

levels of countries and to include more MICs. Countries that are not included in these licence agreements have to pursue other policy options to reduce costs, including the negotiation of reduced prices, and the use of Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities. Countries must carefully assess the impact on public health before entering into trade agreements or World Trade Organization (WTO) accession agreements that contain measures that can delay the entry of generic competition. Overall, a balanced approach is needed that makes ARVs more affordable for LMICs, but which also maintains incentives for companies to further invest in HIV/AIDS research given the relatively small number of pharmaceutical companies that are still conducting research in this area.

The WHO/Joint United Nations Programme on HIV/AIDS (UNAIDS) ARV demand forecasting working group predicted that by the end of 2016 there will be 16.8 million people on ART. Satisfying this demand will require more production capacity for their active pharmaceutical ingredients (APIs). Right now, there are supply constraints for zidovudine (ZDV) and in the near future, supply constraints for lamivudine (3TC) might become a problem. Satisfying the demand for ARVs requires that the market for ARVs in LMICs remains economically viable. This entails that the risks for manufacturers to operate in the ARV market be minimized, which can be achieved by limiting regulatory hurdles, early intelligence sharing on forecasts of ARV demand, improving tender and procurement practices, including timely payment of suppliers, and abandoning the "winner takes all" approach in public tender.

The challenge of dealing with rapidly increasing demand for ARVs represents a great opportunity for manufacturers. These companies have witnessed the value of the LMIC ARV market multiply more than 13-fold in less than 10 years. The number of manufactures with WHO prequalification or US FDA approval for at least one ARV increased from 13 in 2004 to 18 in 2013. At present, the market is concentrated in the hands of a few major players, both on the suppliers' and the buyers' side. This might cause problems for supply security, and become a threat to competition. Managing these threats will require close attention from the main buyers of ARVs in the near future.

Ensuring that ARVs are always in stock can only be achieved if the national procurement and supply management (PSM) system functions without fail at all levels of the health system. In addition, systems need to be flexible enough to manage changes in the treatment regimens used. Unfortunately, the capacity of PSM systems in many LMICs is limited. Consequently, many treatment programmes continue to battle stock-out threats. The Coordinated Procurement Planning (CPP) Initiative, which monitors the supply situation for ARVs in 22 countries, consistently reports around half of its client countries on red alert for imminent stock out. It should therefore come as no surprise that in recent years between 30% and 45% of LMICs annually reported ARV stock outs. Better supply planning and secure funding are the two immediate priority actions that PSM managers need to pursue to prevent stock outs. WHO published a policy technical brief in July 2013 to support supply planning for the introduction of its 2013 consolidated ARV guidelines. Long-term actions should focus on strengthening logistics management systems and the human resource capacity of PSM systems. Countries should consider using the opportunities offered by funding for HIV to strengthen their supply systems more broadly. These initiatives provide a great opportunity to increase the impact of investment in HIV for the health of entire populations.

ART has demonstrated that it can deliver enormous public health benefits, translated into millions of averted deaths and prevented infections. Given the significant decrease of ARV prices and with the renewed commitment of donors, governments and their partners, global access to ART for all patients who need it remains an achievable goal.

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
API	active pharmaceutical ingredient
AMDS	AIDS Medicines and Diagnostics Service (WHO)
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
AZT	zidovudine (also known as ZDV)
BMS	Bristol Meyers Squibb
CHAI	Clinton Health Access Initiative
COBI	cobicistat
CPS	Contracting and Procurement Service (WHO)
CPP	Coordinated Procurement Planning
DNDi	Drugs for Neglected Diseases initiative
d4T	stavudine
DFID	UK Department for International Development
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
EMP	Department of Essential Medicines and other Health Technologies (WHO)
ENF	enfuvirtide (also known as T-20)
ETV	etravirine
EVG	elvitegravir
US FDA	United States Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GFATM	The Global Fund to fight AIDS, Tuberculosis and Malaria
GPRM	WHO Global Price Reporting Mechanism (WHO)
IATT	Interagency Task Team
IQR	interquartile range
JSI	John Snow, Inc.
LMICs	low- and middle-income countries
LIC	low-income countries
LPV	lopinavir
LPV/r	ritonavir-boosted lopinavir
MIC	middle-income countries
MPP	Medicines Patent Pool
MRC	Maraviroc
MSF	Medecins Sans Frontieres
MSH	Management Sciences for Health
USAID	United States Agency for International Development
NMRA	National Medicines Regulatory Authority
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PEPFAR	United States President's Emergency Plan for AIDS Relief
PFSCMS	Partnership for Supply Chain Management System
PPY	per patient per year
PQP	Prequalification of Medicines Programme (WHO)
ppy	per patient per year
PPM	pooled procurement mechanism
PAPWG	Paediatric ARV Procurement Working Group
PSM	procurement and supply management
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir
SCMS	Supply Chain Management System
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TAC	Treatment and Care Team (WHO/HIV Department)
TAF	tenofovir alafenamide
TCO	HIV Technologies and Commodities (WHO)
TDF	tenofovir
TPV	tipranavir
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UMICs	upper-middle-income countries
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNDP	United Nations Development Programme
USAID	United States Agency for International Development
US FDA	United States Food and Drug Administration
VL	viral load
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization
ZDV	zidovudine (also known as AZT)

INTRODUCTION

There has been continued success in scale-up and access to HIV/AIDS treatment in low- and middle-income countries (LMICs) over the past decade. Despite flat-lined international funding, the number of people on antiretroviral therapy (ART) continues to grow annually. In addition, considerable progress has been made in terms of price reductions for a course of ART, a result of global policies and initiatives that have created a more efficient market place. By the end of 2013, more than 11.7 million people were receiving ART in LMICs, representing around one third of all people living with HIV in these countries *(1)*, and the global community's goal of ensuring 15 million people are on treatment by 2015 now seems within reach *(2)*. This is due in large part to the commitments and actions of countries and donors in the scale-up of ART, as well as to generic competition, which has brought steady decreases in the price of ARVs during the past decade. ART scale-up has delivered enormous public health benefits, including millions of averted deaths and prevented infections.

In 2013, the World Health Organization (WHO) released its Consolidated Guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection *(3)*, which increases the number of people eligible for ART globally to 28.6 million. These developments underscore the urgent need to intensify efforts globally to expand access to ART. Whether ART can be expanded to cover their treatment needs depends among others on the extent to which the right ARVs are available and affordable.

In this report we examine global trends in ARV prices and assess how WHO treatment guidelines have influenced the uptake of different ARV formulations. We describe the current constraints limiting the use of second-line and third-line treatments and paediatric treatment, and we explore how the quality of ARVs can be secured and in-country distribution can be improved. This report has been compiled using country-level data reported to WHO on the procurement of ART via the Global Procurement Reporting Mechanism (GPRM) *(4)*, the WHO database on the regulatory status of ART *(5)*, reports on the production capacity for the active pharmaceutical ingredients (APIs) of ARVs *(6)*, the annual WHO surveys on the use of ART *(7-10)*, the *Global AIDS Response Progress Report data (11-15),* the Global Update on the Health Sector Response to HIV 2014 *(1)*, as well as contributions from countries and major stakeholders involved in ART access.

CHAPTER 1. THE DECREASING PRICE OF ARVS

KEY MESSAGES

In the past decade the price of individual ARV formulations has decreased considerably. Rather than continuing to use the least expensive ARVs, treatment programmes in LMICs have used this as an opportunity to replace stavudine (d4T)- based treatment with new and improved first-line medicines. The WHO collates information on the cost of ARVs in the Global Price Reporting Mechanism (GPRM) on public procurement of ARVs in collaboration with GFATM, PEPFAR and international procurement organizations. In the GPRM database, which covers around 75% of all ARV use in LMICs, but which has limitations in recording procurement by upper middle income countries, the cost of first-line ARVs in LMICs registered in GPRM has remained fairly constant. Since 2011, the median annual cost of first-line ART has varied from US$ 117 in 2011 to US$ 115 per patient per year (ppy) in 2013. The price of second-line and third-line ART has also decreased, but less so than first-line treatment, with most LMICs gaining access to second-line treatment for approximately US$ 330 ppy in 2013. Although the price of third-line treatment has decreased for low-income countries (LICs), they still pay more than US$ 1500 ppy for a combination of raltegravir (RAL), etravirine (ETV) and darunavir (DRV). Middle-income countries (MICs) pay considerably higher prices. Whereas all LICs and most MICs can access these prices, there are MICs that pay higher prices – typically Brazil and Eastern European countries, such as Kazakhstan, the Russian Federation (now a high-income country) and Ukraine. Higher prices have also been documented in other Latin American and Asian countries, including China. The inability of these countries to access cheaper generic versions of the ARVs is a key factor in explaining why their prices remain higher.

The WHO collates information on the procurement of ARVs in the Global Price Reporting Mechanism (GPRM), in collaboration with GFATM, PEPFAR and international procurement organizations, including, UNICEF, IDA, MissionPharma, CHAI and UNITAID. The GPRM database covers and reports publicly on around 75% of all ARV procurement in LMICs, but has limitations in recording procurement by upper middle income countries. As upper middle income countries, which most often don't channel their procurement through the international procurement organizations which contribute data to the GPRM, and the latter is the main source of pricing information in this report, it is recognized that procurement of ARVs by upper MICs is underrepresented. When information on their – often higher – prices is available, it is acknowledged in the report.

ADULT FIRST-LINE ART

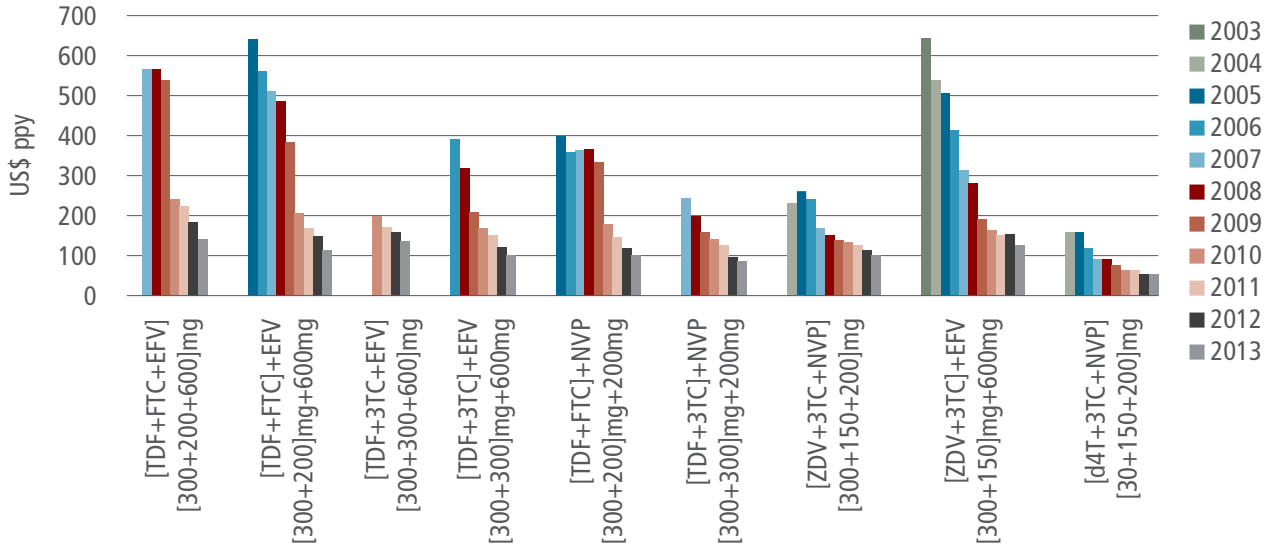
The price of the most commonly used first-line ART regimen in LMICs between 2004 and 2013 has decreased considerably over the past decade (Figure 1.1). The impact on the medicines cost in treatment programmes has been salutary: as the price of newer and less toxic regimens decreased, treatment programmes in LMICs have gradually replaced older, less expensive regimens such as d4T + lamivudine (3TC) + nevirapine (NVP) with better but slightly more expensive regimens such as zidovudine (AZT) + 3TC + NVP, and later with tenofovir (TDF) + 3TC or emtricitabine (FTC) + efavirenz (EFV). Consequently, the price paid for WHO recommended first-line ARVs in LMICs, weighted for the volume of their sales in GPRM, has remained fairly constant since 2011, varying between US$ 117 in 2011 and US$ 115 ppy in 2013 (Figure 1.2).

Because generic suppliers globally now have a market share of more than 98% of the donor-funded ARV market, their price levels determine the median price of the first-line treatment in LMICs. Therefore, in 2013 the cheapest WHO recommended first-line regimen could be administered for a median price of < US$ 100/year (interquartile range [IQR] 96.1–113), when using the two-drug FDC of TDF + 3TC, plus a single drug tablet of EFV. The median prices of alternative first-line treatment regimens, when formulated with at least one tablet as a FDC, as well as the median price of TDF + 3TC + NVP and zidovudine (ZDV) + 3TC + NVP, are shown in Figure 1.3.

Regimens containing 3TC are less expensive than those containing emtricitabine (FTC), and three-drug FDCs are more expensive than combining a two-drug FDC + EFV. The reason why three-drug FDCs are more expensive is not clear, because three-drug FDCs require less packaging material, contain the same amount of APIs as two-drug FDCs + EFV, and should take less time to manufacture than two single tablets.

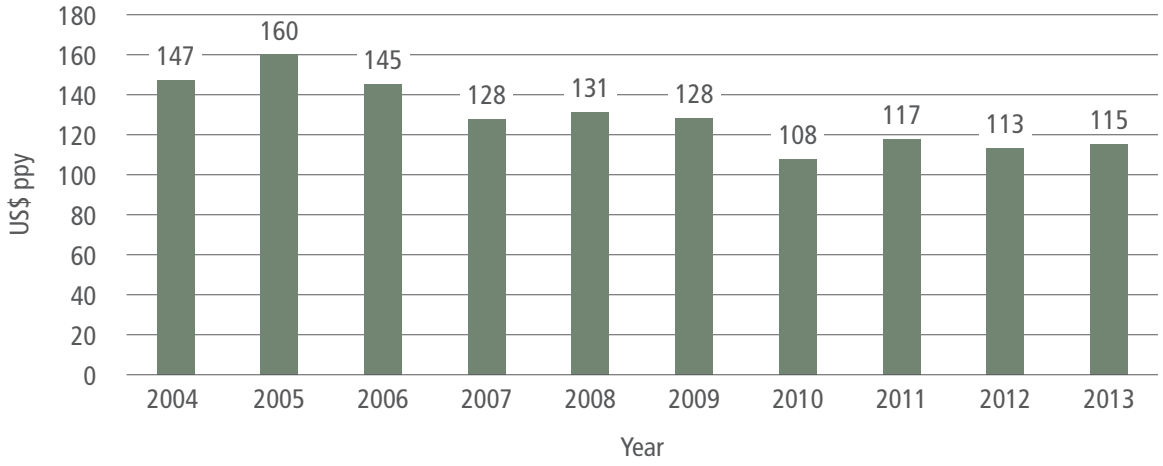
Regimens combining TDF with the less preferred NVP instead of EFV are slightly cheaper than regimens containing EFV. However, NVP requires a twice-daily administration. This makes the regimen more difficult for patients to adhere to, which renders it less effective and more likely to generate HIV drug resistance. In addition, NVP is more toxic than EFV in people with less advanced HIV infection. This makes NVP-containing regimens less useful for increasing coverage among pregnant women

Figure 1.1 Median price (US$ ppy) of the main ART regimens used in LMICs, 2003–2013



Source: GPRM.

Figure 1.2 Median price (US$ ppy) of the mix of first-line ART regimens used, weighted by volume of sales, 2004–2013



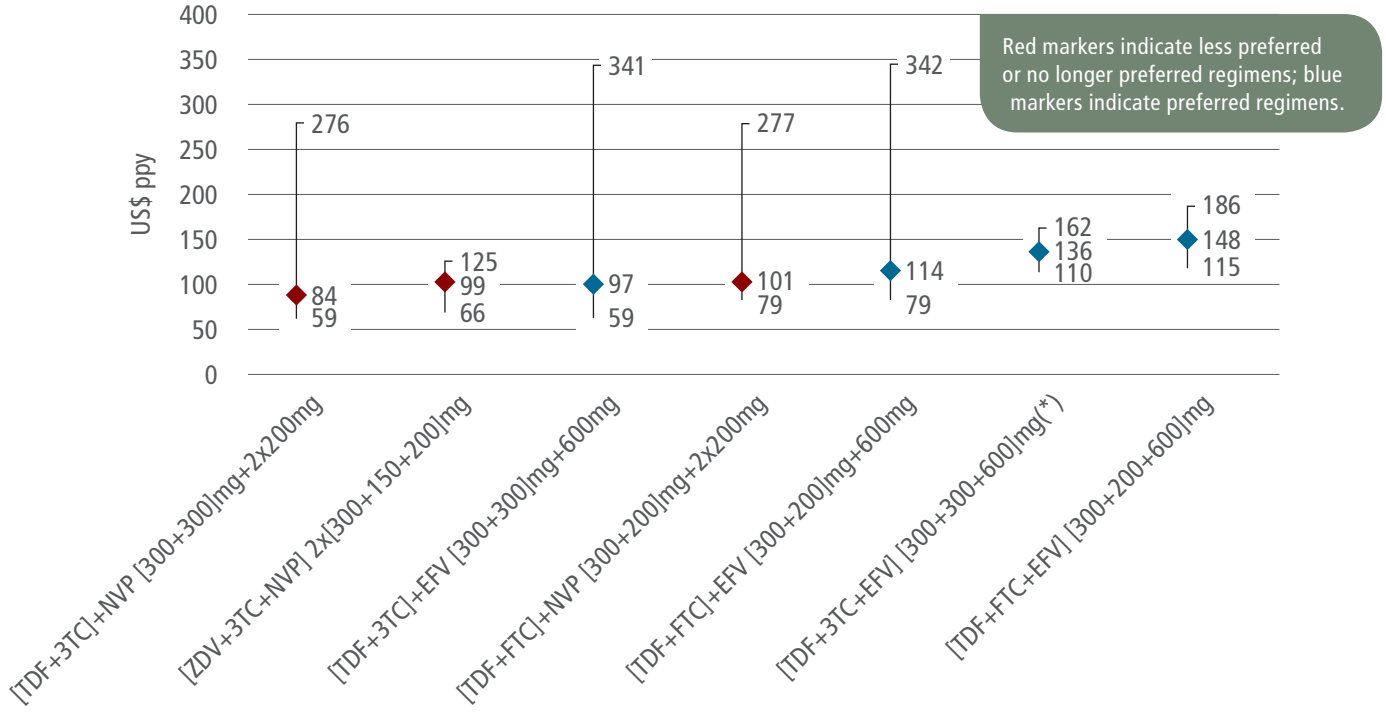
Data include drugs administered as a three-drug fixed-dose combination (FDC), a two-drug FDC, and single drug formulation tablets.

Source: GPRM.

and people with higher CD4 cell counts, who should be accessing ART in increasing numbers. However, NVP will still have a place in the treatment arsenal as an alternative for people who develop toxicity to EFV. Finally, the regimen ZDV + 3TC + NVP, no longer recommended as a first-line regimen by WHO but still in use in many LMICs in first-line treatment, has as additional drawbacks a higher toxicity of ZDV compared with TDF, but is included in Figure 1.3 to show that, compared with TDF + 3TC plus a tablet of EFV, it is no longer less expensive. WHO and partner organizations have developed a policy brief on transition to new treatment regimens for guidance for procurement planning *(16)*.

While the price of different first-line ART regimens evolved in a relatively narrow band, high prices are sometimes paid. High-cost outliers comprise less than 4% of the 2013 transactions in the GPRM data set, in which data from upper MICs are underrepresented. It should thus be noted that a recent WHO report documented that Brazil, China, Cuba, Ecuador, Kazakhstan, the Russian Federation, Thailand and Ukraine paid prices in excess of US$ 300 ppy for first-line treatment regimens in 2012 – in the case of Brazil, Kazakhstan and the Russian Federation more than US$ 1000 ppy *(17)*. The main determinant explaining these higher prices is countries sourcing the drugs from the originator companies when part or all drugs in the treatment regimen are patent protected.

Figure 1.3 Median price and range (US$ ppy) of WHO recommended and alternative first-line treatment regimens in LMICs, 2013



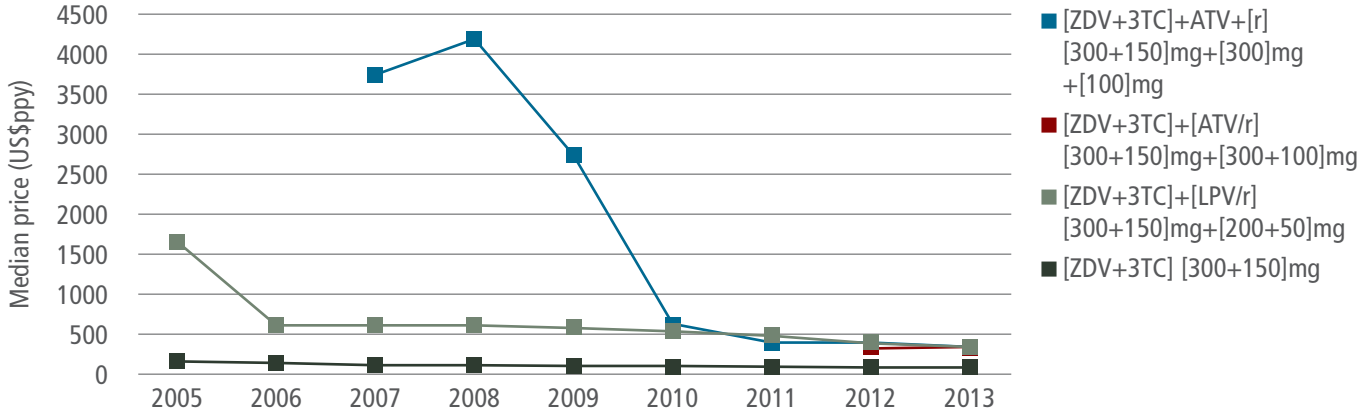
*1 outlier excluded (US$ 1221 ppy, Belarus, supplier Merck Inc.).

Source: GPRM.

Adult second-line ART

The WHO 2013 consolidated guidelines WHO now recommends that people who fail first-line treatment with TDF + 3TC or FTC + EFV be given AZT + 3TC plus either ritonavir (RTV)-boosted lopinavir (LPV/r) or RTV-boosted atazanavir (ATV/r) *(3)*. Figure 1.4 shows the price evolution of these second-line regimens, which are nearly always administered as a FDC of AZT + 3TC with either LPV/r or ATV with RTV (prior to 2012), or ATV/r (when this FDC became available in 2012). The price of AZT + 3TC is also indicated, illustrating the relative dominance of the protease inhibitor component in the price of the regimen.

Figure 1.4 Price evolution of second-line treatment regimens in LMICs (US$ ppy), 2005–2013



Source: GPRM.

As a result of the decreasing price of the protease inhibitors, most LMICs can now gain access to second-line treatment for around US$ 330 ppy. As for first-line drugs, there are MICs that pay more. The WHO report on prices paid for ARVs by MICs documented that in 2012 Brazil, China, Indonesia and Ukraine paid > US$ 500 ppy, Kazakhstan US$ 1800 ppy, and the Russian Federation > US$ 4000 ppy. Regimens containing LPV/r procured from the originator company resulted in higher pricing for these six countries.

Adult third-line ART

While WHO does not explicitly recommend a third-line regimen (or "salvage" treatment) at present, it does recommend that such regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, for example, integrase inhibitors, second-generation non-nucleosides and protease inhibitors *(3)*. WHO advises that countries considering a third-line regimen should include darunavir (DRV) boosted with ritonavir, raltegravir (RAL) and etravirine (ETV) *(3)*. Table 1.1 shows the median prices paid for third-line treatment in LMICs. The higher prices, compared with first-line and second-line drugs, can be explained by the fact that these drugs are new to the market and more widely patented. In addition, the size of the market for third-line treatments is currently small.

Because of the discounted pricing of their drugs by the originator companies, the median prices of DRV (300 mg formulation only), ETV and RAL have decreased considerably in the past few years in LICs. According to the GPRM database, the lowest price in these countries in 2013 was US$ 664 ppy for DRV, US$ 439 ppy for ETV and US$ 553 ppy for RAL. While this certainly represents progress, the reality is that the cost of the three drugs added up still comes to more than US$ 1500 ppy. In addition, MICs and countries outside sub-Saharan Africa, which do not benefit from those discounts, face much higher prices. In these countries DRV (median price US$ 5180 ppy in 2013) remains very expensive. Access to other drugs that WHO has not yet recommended in its treatment guidelines but which some MICs use as part of salvage treatment – tipranavir (TPV) [US$ 6072], maraviroc (MRC) [US$ 5190] and enfuvirtide (ENF) [US$ 17 170]) – also remains a challenge because of their high price (Table 1.1).

Table 1.1 Median prices (US$ ppy) paid for third-line drugs by LMICs, 2008-2013

	2008	2009	2010	2011	2012	2013
DRV (600 mg)	NA	NA	3833	3287	5215	5180
DRV (300 mg)	NA	5805	1123	1013	732	664
ETV (100 mg)	NA	1173	1178	854	854	439
RAL (400 mg)	NA	NA	980	973	883	553
TPV (250 mg)	10037	10037	6560	7047	6072	6072
MRC (150 mg)	NA	NA	NA	NA	5177	5190
ENF (90 mg)	24100	24100	20700	20401	17071	17170

NA, not available.

Source: GPRM.

Paediatric treatment

WHO recommends that infants and children aged less than three years should start ART with a regimen containing LPV/r *(3)*. If LPV/r is not available, treatment should be initiated with an NVP-based regimen. In both cases, the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone for the ART regimen should be ABC + 3TC or AZT + 3TC. Figure 1.5 shows the price evolution of the WHO-recommended first-line regimens for children aged less than 36 months (at a defined daily dose recommended for a child with a body weight of 10 kg). For reference purposes, the price of the d4T-containing regimen (d4T + 3TC + NVP), which is recommended only in special circumstances, is also shown.

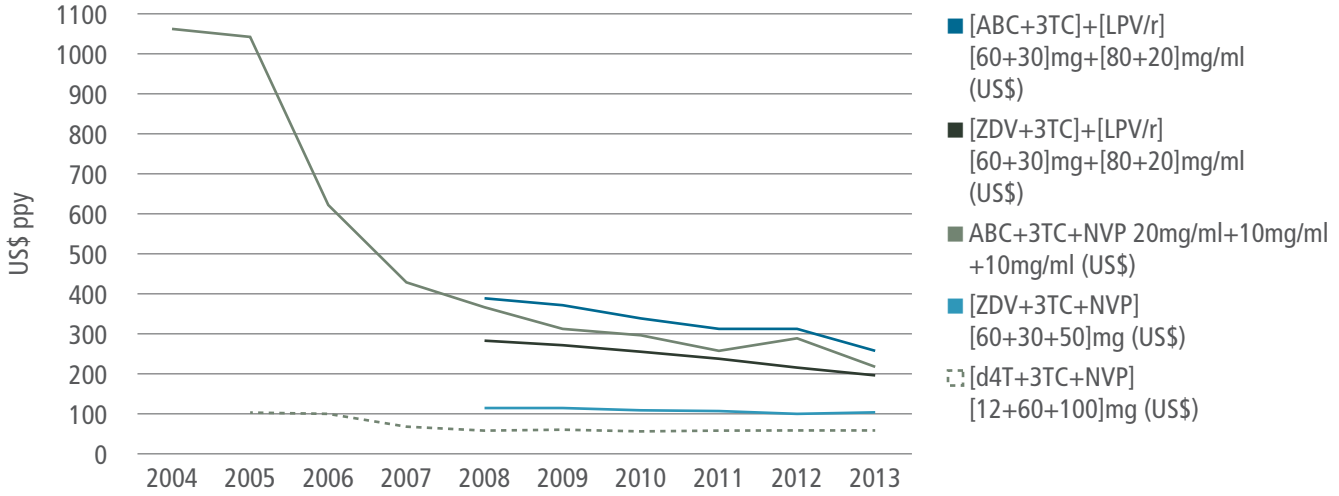
As with adult treatment, the median price of paediatric regimens also decreased over time. In 2013, for the first time, a regimen containing LPV/r with AZT + 3TC became available for less than US$ 200 ppy. However, this is still substantially more than the price of AZT + 3TC + NVP, the most frequently used regimen in paediatric treatment, the median price of which was US$ 97 ppy in 2013.

In recent years, new formulations that meet the unique administration needs of children have become available, notably dispersible FDCs of ABC + 3TC and ZDV + 3TC, which can be dispersed in liquid before administration. These products have significantly improved the quality of paediatric HIV care in LMICs, without increased costs.

For children aged 3 years to 10 years (with a body weight of 10–25 kg), EFV is preferred to NVP. In addition, the NRTI backbone for an ART regimen should be, in preferential order, ABC + 3TC, or AZT + 3TC, or TDF + 3TC (or FTC) *(3)*. The prices of those regimens have also come down over the past decade. In 2013, the median price paid for ABC + 3TC + EFV for a child with a body weight of 25 kg was US$ 201 ppy, almost US$ 90 ppy more than the US$ 112 ppy paid for a regimen containing ABC + 3TC + NVP, and more than US$ 100 ppy more than the US$ 97 ppy paid for a regimen containing AZT + 3TC + NVP. The availability of the latter regimen as a three-drug FDC and its lower cost may explain why it is the most widely used regimen at this time.

As is the case for adult ART, some MICs pay considerably more for their paediatric ARVs than the median prices presented here. The WHO report on MIC country ARV prices *(17)* documented much higher prices in China, Kazakhstan, the Russian Federation and Ukraine than in LICs and countries able to access generic ARVs.

Figure 1.5 Median price (US$ ppy) of paediatric first-line treatment regimens (standardized for a body weight of 10 kg), 2004–2013



Source: GPRM.

CHAPTER 2. IMPACT OF WHO TREATMENT RECOMMENDATIONS ON ARV USE

KEY MESSAGES

Since 2001, as new clinical evidence and drug formulations have emerged, five sets of new clinical guidelines for treatment of HIV/AIDS have been issued by WHO. These guidelines have had a direct effect on the use of key ARVs in LMICs. Positive developments include the increased use of TDF and EFV in first-line treatment – at the end of 2012, almost half of all people using ART in LMICs had TDF in their treatment regimen, and 50% used EFV. The uptake of second-line and third-line treatment regimen in LMICs remains low, despite guidelines changes, with likely factors for this limited uptake being the inability to diagnose treatment failure. Of concern, however, is the development and delivery of ARV formulations tailored for children, which still lags behind that of adults. The uptake of LPV/r now recommended by WHO as the drug of choice in children aged less than three years is low: it is limited to less than 3% of children in 2013. Limited diagnostic capacity is the most likely explanation for its low uptake. WHO and its IATT partners recently published a list of optimal paediatric ARV formulations to reduce market fragmentation and streamline procurement for paediatric ARV medicines. In addition, DNDi and Cipla Ltd are working on the development of new more user-friendly LPV/r formulations with support from UNITAID. Other formulations are urgently needed (ie. ATV/RTV, DRV/RTV, TDF/XTC/EFV) and some are currently under consideration (ie. ABC/3TC/EFV) by the Paediatric ARV Working Group.

In the past decade WHO's recommended guidance on which treatments should be used to treat HIV/AIDS has developed in accordance with new clinical evidence and the development of new drugs. The first ART guidelines were issued in 2001 *(18)* and since then have been updated four times *(19–21, 3)*. In addition, in 2011, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the treatment 2.0 initiative with the aim of promoting improved treatment protocols for people living with HIV *(22)*.

ADULT ART

Following strong advocacy calling for the development of "one pill once a day", as part of the treatment 2.0 initiative, several well-publicized meetings on the use of TDF and d4T in 2011 *(23)*, and considerable evidence review, the 2013 revision of the WHO treatment guidelines *(3)* recommended TDF + (3TC or FTC) + EFV as the preferred first-line treatment regimen. Additionally, WHO has recommended that d4T should be phased out since 2006, and restated this recommendation in 2010 and 2013.

Figure 2.1 shows the relationship between these recommendations and market share of different nucleosides/nucleotides in LMICs between 2004 and 2013. The market share of d4T decreased from 77% in 2005 to 2% in 2013, while TDF's market share increased from < 1% in 2005 to 61% in 2013. Countries had started switching to TDF-containing regimens before WHO formally stated its preference for TDF over AZT, as part of their phasing out of d4T, but after 2011, with advocacy for the use of "one pill once a day" and the informally stated preference for TDF, the latter started eroding the market share of ZDV.

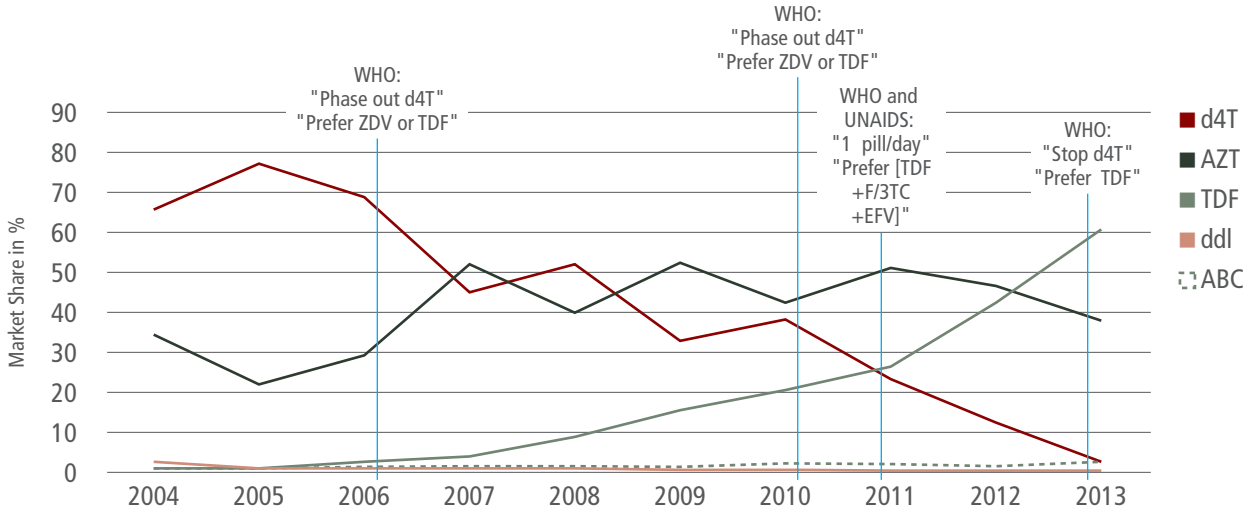
A factor enabling the increasing number of generic manufacturers offering TDF-based FDCs is the work of the WHO Prequalification of Medicines Programme (PQP). Figure 2.2 highlights the number of generic manufacturers offering TDF-containing FDCs prequalified by WHO. This increased number stimulated competition between manufacturers and resulted in lower prices for TDF-containing products. Extrapolating the 77% of sales to LMICs recorded in the GPRM to the entire LMIC market, we estimate that at the end of 2012, 4.2 million people were using an ART regimen containing TDF; likewise, in 2013, the number of patients will likely increase to around 6.5 million.

In parallel with the increased uptake of TDF, the uptake of FTC increased from < 1% in 2007 to 16% in 2013. 3TC remains the dominant cytidine analogue drug, present in 84% of all ART regimens in 2013. The resilience of 3TC in ART is explained by its presence in most FDCs such as TDF with 3TC, and because WHO considers 3TC to be therapeutically equivalent to FTC. In addition, 3TC-containing FDCs are about US$ 10 ppy cheaper than FDCs containing FTC.

With the recommendation to use EFV as part of the preferred first-line ART regimen, the proportion of people using EFV as part of their ART regimen increased from 20% to 30% between 2005 and 2010, and to 50% in 2013.

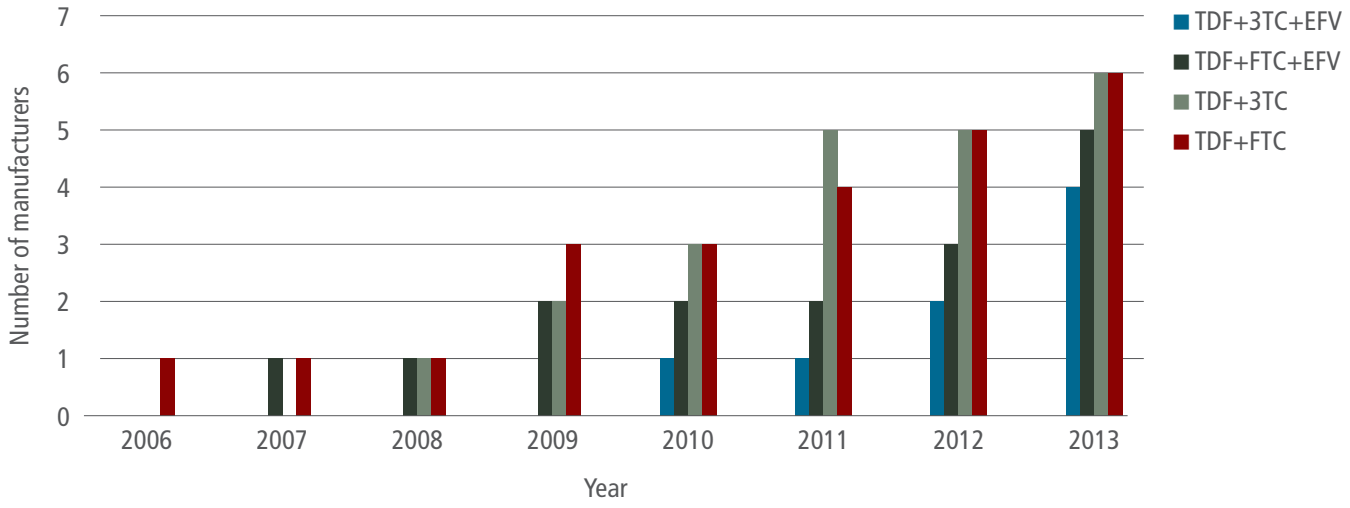
In second-line treatment, WHO recommends the use of a protease inhibitor – either LPV/r or ATV/r – with 3TC and a nucleoside that has not been used in first-line treatment *(3)*. WHO's 2013 ARV use survey also documented that at the end of 2012 around 4% of patients on ART in LMICs were on second-line ART *(10)* – varying between 2.3% and 3.8% of patients in the past 5 years. Additional findings

Figure 2.1 Market share (%) of nucleoside/nucleotide ARVs (except 3TC and FTC) in LMICs, 2004–2013



Source: GPRM.

Figure 2.2 Number of WHO prequalified or US FDA[1] approved generic manufacturers of TDF-containing fixed-dose combinations, 2006–2013



Source: WHO PQP database.

from this survey indicate that LPV/r followed by ATV/r are the main protease inhibitors in use, and that other protease inhibitors are either disappearing from the market or have limited sales to date.

While cost is often cited as the explanation of the limited uptake of second-line treatment, it is only part of the explanation. In countries with access to viral load (VL) testing, the uptake of second-line and third-line treatment is much higher. Several countries (among others, Kenya and Uganda) are now rolling out programmes to make VL testing available to all patients in their treatment programmes, using dried blood spots and innovative transport and communication mechanisms to support expansion. In the near future it is expected that simpler technologies will enable decentralization of VL testing (Box 2.1).

Data on the uptake of third-line ART in LMICs are limited. Although WHO does not yet recommend a third-line treatment regimen, it advises that countries considering a third-line regimen should include DRV boosted with ritonavir, RAL and ETV *(3)*. As of March 2014, the number

1 Producers with WHO Prequalification or with US FDA approval are both considered as both can be procured from Global Fund grants and by the UN.

Box 2.1 Access to VL testing

More than six VL and early infant diagnosis point of care products will emerge over the next three years, including platforms that allow for multiple types of laboratory tests to be performed on one device. UNITAID supports their rapid introduction, with a commitment of over US$ 120 million since 2013. The countries supported are largely in sub-Saharan Africa, where a significant proportion of HIV-affected populations live in rural areas, and where there is the greatest need for access to appropriate point-of-care diagnosis. Full scale-up to enable country HIV testing targets and market impact targets (such as sustainable production at scale and price reductions) to be met for point-of-care diagnostics, will require complementary funding from financing mechanisms such as the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) and the United States President's Emergency Plan for AIDS Relief (PEPFAR).

Source: text contributed by UNITAID.

of patient-years of treatment reported in the GPRM was 429 for DRV, 317 for RAL, and 110 for ETV – but MICs are underrepresented in GPRM. Some are known to use these drugs in much higher numbers of patients. For example, in 2012 in Brazil there were 5835 people on DRV, 6017 on RAL and 594 on ETV. Likely factors for the limited uptake of third-line ARVs in LMICs are the inability to diagnose treatment failure in these settings, and the high cost of third-line treatments.

PAEDIATRIC ART

WHO recommends that infants and children aged less than three years should start ART with a regimen containing LPV/r *(3)*. If LPV/r is not available, treatment should be initiated with an NVP-based regimens. In both cases, the NRTI backbone for the ART regimen should be ABC + 3TC or AZT + 3TC. For first-line ART in children aged three to 10 years, EFV is preferred to NVP, and the NRTI backbone for an ART regimen should be, in preferential order, either ABC + 3TC, or AZT + 3TC, or TDF + 3TC (or FTC)[3].

Unfortunately the development of treatments tailored for children, and their delivery, has lagged behind that of adults. A recent initiative launched by UNITAID, DNDi and the MPP will seek to address this by channelling efforts to the development of the needed WHO-recommended formulations. Figure 2.3 shows how the uptake of different paediatric treatment regimens evolved over time in 12 countries that responded to the WHO global surveys on ARV use between 2010 and 2013 *(7–10)*. The findings from these surveys show that there has been a consolidation towards three treatment regimens: AZT + 3TC + NVP, AZT + 3TC + EFV and ABC + 3TC + NVP. The decreasing use of d4T mirrors the WHO recommendation to phase it out. This raises concerns around which manufacturers are going to ensure production of the minimal quantities of d4T products that will be needed in the future to treat children that cannot receive AZT nor ABC and will have no other choice but to use d4T-based regimens.

The use of LPV/r is low, meaning that major change is needed to ensure scale-up of treatment to very young children in accordance with the 2013 guidelines *(3)*. In the 96 countries that responded to the survey in 2013 *(10)*, only 3% of children were using LPV/r as part of their treatment regimen. With the new WHO recommendations in 2013 on the use of ART *(3)*, and increased efforts in scaling up early infant diagnosis, increased LPV/r use is expected in the near future. The arrival of a more user-friendly formulation of LPV/r (known as minitabs or pellets), under development might also result in increased uptake (Box 2.2). Other formulations are urgently needed (ie. ATV/RTV, DRV/RTV, TDF/XTC/EFV) and some are currently under consideration (ie. ABC/3TC/EFV) by the Paediatric ARV Working Group.

Box 2.2 Developing new LPV/r formulations for infants and children

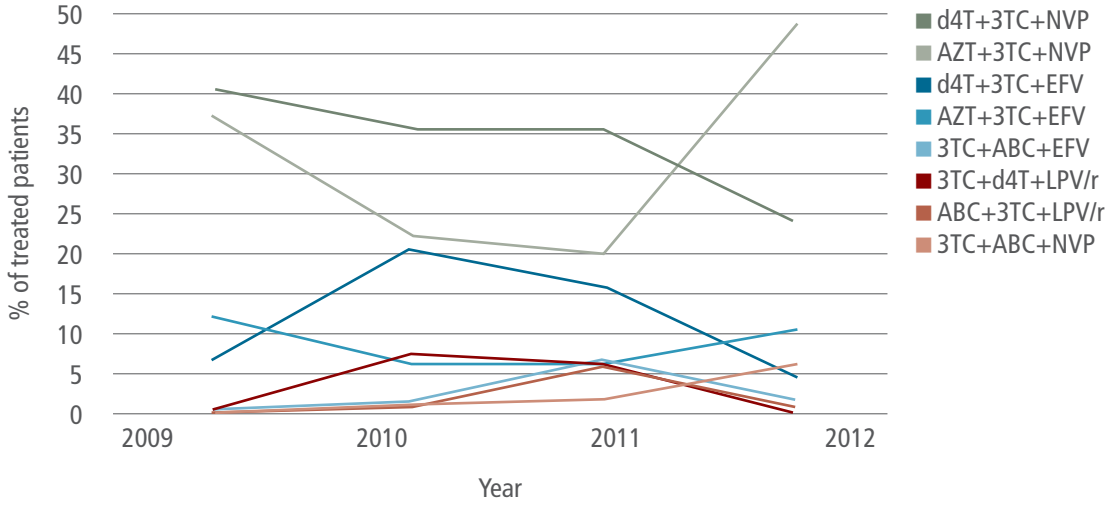
Currently available paediatric formulation of LPV/r is a liquid with a high alcohol content. It has a poorly tolerated taste, is difficult to administer, and carries a high risk of dosing errors. In addition, it has a short shelf-life, requires a cold chain, and is voluminous and expensive. The pellets single strength which will overcome the cold chain requirements and will hopefully increase uptake may become available in 2015 and are produced by Cipla Ltd. With the support of UNITAID, DNDi is currently working with the Indian generic company, Cipla Ltd, to develop two solid "4-in-1" FDC treatments. The two 4-in-1 combinations are AZT+3TC+ LPV/r and ABC+3TC+ LPV/r. An additional formulation of RTV is also being developed. The goal is to make these new formulations available by 2015. The new 4-in-1 paediatric formulation will be in the form of solid granules that fit into a capsule, also referred to as "sprinkles". Caregivers will be able to open the capsules and give the granules to children with soft food or breast milk. They will not require refrigeration, and they will be taste-masked and easy to dose.

Source: text contributed by UNITAID.

Another key feature of the paediatric ARV market is the welcome shift towards solid formulations. WHO strongly endorses the use of dispersible FDCs to simplify dosing for providers and patients and to improve adherence outcomes *(3)*. With the arrival of the new formulations, the proportion of children using liquid formulations as part of their treatment regimen has declined over time. This was possible initially because solid FDCs of d4T were introduced in 2006, and after 2008 with the introduction of FDCs containing AZT (and to a lesser extent ABC). However, progress in their uptake has been too slow, which hinges on the inability of some MICs to access generic products, the failure of producers to seek regulatory approval for their FDCs in small markets, and a lack of awareness among providers and programme managers about the availability of paediatric FDCs. In addition, the proliferation of these newer options alongside the continued availability of older suboptimal products in the small market of paediatric ARVs has resulted in fragmentation of procurement orders across multiple products.

To counter this fragmentation, WHO has now, in collaboration with the Interagency Task Team (IATT) on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children, formulated a list of optimal paediatric ARV formulations (Table 2.1). This list is restricted to products that are currently approved and available for procurement and does not include products in the development pipeline. This list will be reviewed on a regular basis.

Figure 2.3 Evolution of the major paediatric first-line ART regimens used, 2009– 2012



Source: WHO global surveys on ARV use 2010–2013 *(7–10)*.

Table 2.1 IATT optimal list of paediatric ARV formulations

Drug class (or FDC)	Product	Formulation	Dosage	Rationale for list
NRTI	AZT	Oral liquid	50 mg/5 ml	For infant prophylaxis to prevent mother-to-child transmission
NNRTI	EFV	Tablet (scored)	200 mg	For first-line treatment
NNRTI	NVP	Tablet (dispersible, scored)	50 mg	For first-line treatment
NNRTI	NVP	Oral liquid	50 mg/5 ml	For infant prophylaxis to prevent mother-to-child transmission
Protease inhibitor	LPV/r	Tablet (heat stable)	100 mg/25 mg	For second-line treatment
Protease inhibitor	LPV/r	Oral liquid	80/20 mg/ml	For second-line treatment
FDC	AZT/3TC	Tablet (dispersible, scored)	60/30 mg	For first-line treatment
FDC	AZT/3TC/NVP	Tablet (dispersible, scored)	60/30/50 mg	For first-line treatment
FDC	ABC/3TC	Tablet (dispersible, scored)	60/30 mg	For first-line treatment
FDC	ABC/3TC/AZT	Tablet (non-dispersible, scored)	60/30/60 mg	For first-line treatment

Source: IATT *(24)*.

CHAPTER 3. QUALITY ASSURANCE AND REGULATION

KEY MESSAGES

Regulatory control in LMICs to ensure the quality of ARVs is limited, both for adult and paediatric formulations. The explanations likely include that their regulatory authorities are under-resourced, and that the manufacturers have little incentive to comply with the national regulatory process when they can sell their products anyway without regulatory approval. The WHO Prequalification of Medicines Programme (PQP) and the US FDA approval process (tentative when there is still patent or exclusivity market protection for the product in the USA) provide up-front quality guarantee for the list of prequalified ARVs that the GFATM- and PEPFAR-supported countries can procure. The WHO PQP and the US FDA programme opened the market to generic suppliers and were instrumental in enabling the decreasing prices of ARVs seen in the last decade. They also enabled the introduction of several important formulations, which presently are not available in countries where part or all of their content is protected by patents. However, as countries are increasingly buying their own ARVs, this is not a sustainable solution. For sustainable access to high-quality ARVs, countries should urgently strengthen the capacity of their national medicines regulatory authorities. In addition, to enable the rapid introduction of new formulations in their markets, it is important that their processes be simplified. The WHO PQP and the African Medicines Regulatory Harmonization initiative are both working to support this.

Governments have the responsibility to ensure that the manufacture, distribution and use of medicines are regulated effectively. The regulation of medicines and medical products covers all measures – legal, administrative and technical – that governments take to ensure the safety, efficacy and quality of medicinal products *(25)*. This includes, among others:

- licensing the manufacture, import, export, distribution, promotion and advertising of medicines and medical products;
- assessing the safety, efficacy and quality of medicinal products;
- issuing marketing authorization, inspecting and conducting surveillance of manufacturers, importers, wholesales and dispensers of medicines and medical products;
- controlling and monitoring the quality of medical products on the market;
- controlling the promotion and advertising of medicinal products, and providing independent information on medicines to professionals and the public.

Implementing effective medicines regulation is a huge task, and, in view of capacity constraints, countries will in many cases accept data and assessments on the manufacture, safety, efficacy and quality of medicines from regulatory authorities in other countries to decide whether to license the use of medicines in their country. The issue of medicine quality is of particular concern in countries in which regulatory oversight is weak and where official supply channels fail to reach patients *(25)*.

On the other hand, capacity constraints in regulatory authorities can also have as a consequence that medicines that are needed are not available in the country, or available from one supplier only, which creates monopolies and most often has as a consequence that prices are too high. One way around this constraint is to authorize the use of unlicensed products regardless of their approval status – with a waiver of regulatory approval – on the basis of the credibility of their producers. However, this is a stop-gap measure, because it makes it more difficult to assert the authority of national regulators in the quality control and distribution of those medicines.

REGULATORY STATUS OF ARVS IN LMICS

The WHO ARV drug regulatory database records regulatory approvals in place for all ARVs *(5)*. The database is updated annually with information contributed on a voluntary basis by WHO-prequalified or US FDA tentatively approved manufacturers. While not exhaustive, the database gives a fairly comprehensive view of the extent to which drug regulatory approvals have been obtained, for which drugs, by which manufacturers, and in which countries.

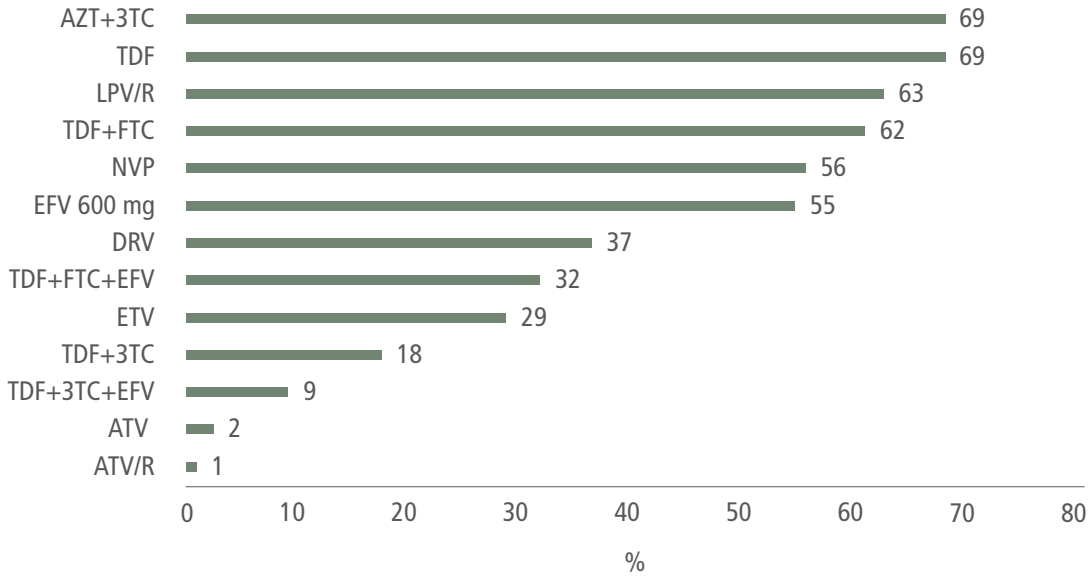
Figure 3.1 shows the percentage of 139 LMICs with regulatory approvals on record in the 2013 update of the WHO ARV drug regulatory database for at least one producer of the 14 most commonly used ARV formulations. On average, only 36% of ARVs were on record as having at least one manufacturer with drug regulatory approval in place.

Figure 3.2 shows a similar pattern with respect to drug regulatory approvals for paediatric formulations – the main difference with the regulatory status of adult formulations being that the average approval rate for paediatric formations is even lower: 18%, compared with 36% for adult formulations. According to the 2013 update of the

WHO ARV drug regulatory database, regulatory approval rates were higher for the older (and less preferred) liquid formulations than for solid formulations. As a consequence of the limited extent to which paediatric formulations are formally registered, on average only 25% of LMICs have regulatory approvals in place to administer at least one of the WHO preferred or alternative paediatric regimens (either ABC + 3TC or AZT + 3TC + LPV/r).

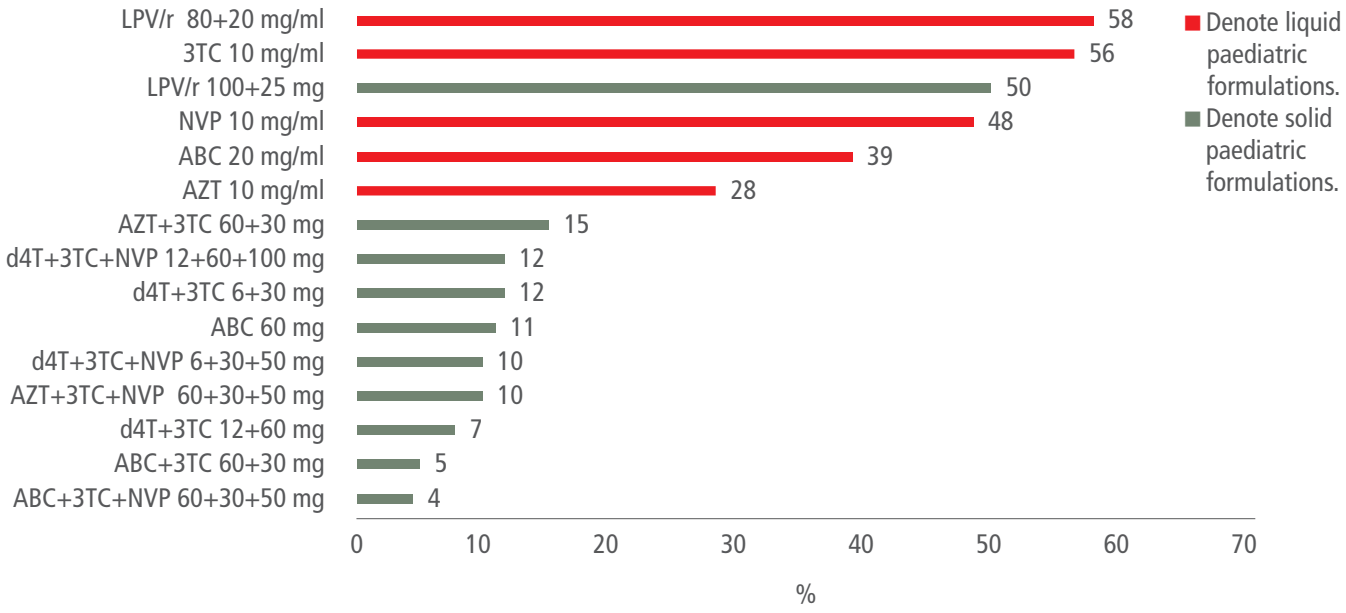
Taken together, these data suggest that the great majority of ARV drugs in LMICs are being used without formal regulatory approval at the national level. The explanations likely include that their regulatory authorities are under-resourced, and that the manufacturers have little incentive to comply with the national regulatory process when they can sell their products anyway without regulatory approval. However, the consequence is that this also impedes the

Figure 3.1 Percentage of 139 countries with at least one registered producer of key adult ARV formulations, 2013



Source: WHO ARV drug regulatory database, updated 2013 *(5)*.

Figure 3.2 Percentage of 139 countries with at least one registered producer of key paediatric ARV formulations, 2013



Source: WHO ARV drug regulatory database, updated 2013 *(5)*.

ability of the national regulators to play their role in quality assurance of the medicines being distributed and used in their country. Both the GFATM and PEPFAR require either WHO prequalification or US FDA (tentative) approval of the ARV drugs that their support makes available, and ensure that drug quality is assessed after arrival in the countries where they will be used. Likely this is why, so far, few problems have been reported with regards to the quality of ARVs during the past 10 years. However, this is only as sustainable as their funding will stretch. As countries are increasingly paying for their own medicines, it is important that they improve their regulatory oversight of ARVs – and likely other medicines.

DRUG REGULATION INITIATIVES

In response to the increasing need for quality-assured ARTs, and the imperative to make them affordable for LMICs, WHO established the PQP in 2001. The PQP assesses the quality of WHO-recommended medicines for procurement by United Nations (UN) agencies and GFATM. The Programme prequalified the first generic ARV drugs in 2002. The fact that the PQP was open to generic producers proved crucial in improving access to ART in LMICs. Until then, triple ART cost around US$ 12 000 ppy. By prequalifying generic ARVs, WHO ensured that patients in LMICs could access ART at low prices when the price of ART decreased rapidly following the increased number of prequalified generic producers.

Following WHO's example, the US FDA launched a fast-tracked review process to enable the use of generic ARVs by PEPFAR in 2004. When there is still patent or exclusivity market protection for the product in the USA, the FDA gives the product tentative approval, which authorizes PEPFAR to purchase the product for use in LMICs. For products that have been successful in the FDA approval process, manufacturers do not need to resubmit the same products to WHO for prequalification. This mechanism avoids duplication of efforts and widens the choice of quality-assured ARVs for procurement.

As of March 2014, WHO has prequalified over 200 ARV formulations *(26)* and the US FDA has approved 170 ARV formulations *(27).* The market share, by volume, of generic manufacturers in LMICs increased consequently, from next to none in 2001 to more than 98% in 2012. The competition between manufacturers, coupled with high-volume purchases by GFATM, PEPFAR, and later UNITAID, has brought the annual cost of AIDS medicines to < 1% of the price in 2000. In 6 years of procuring ARVs for PEPFAR, PfSCMS made savings of more than US$ 1 billion, primarily through generic procurement *(28).* However, savings were not the only effect: by empowering generic manufacturers to supply ARVs, WHO prequalification and the approvals by the US FDA also enabled the introduction of FDCs for adults, and paediatric combination products which high-income countries could not access because of patents. The first FDC to be prequalified by WHO in 2003 was d4T + 3TC + NVP, three years ahead of the US FDA. Other FDCs that many LMICs can access, but patients in high-income countries where patent rights are enforced cannot access, include among others TDF + 3TC + EFV, AZT + 3TC + NVP, ATV/r, and the dispersible paediatric formulation of ABC + 3TC.

ACCELERATION OF REGISTRATION MECHANISMS

Given the importance of functioning regulatory control for sustainable access to ART, work to overcome the capacity constraints in national drug regulatory authorities and to simplify their regulatory approvals process is on-going.

In 2012, the PQP launched a collaborative procedure with a number of national medicines regulatory authorities (NMRAs) aimed at fast-tracking registration of WHO-prequalified medicines in countries where the medicines are needed. Fifteen countries are now participating in the initiative, which has seen faster registration of ARVs, among other products. Through this initiative, manufacturers of a prequalified product can authorize PQP to share its assessment and inspection information with NMRAs in countries in which registration is sought. If the NMRA agrees to apply the procedure to the specific product, it commits to issuing its independent decision within 90 days. If the decision is positive, then the product can be marketed immediately for the benefit of patients.

The leadership of the African Union, in collaboration with development partners, established the Pharmaceutical Manufacturing Plan for Africa in 2007 *(29).* This ambitious Plan aims to expand access to medicines on the continent and hinges on strengthening national regulatory authorities in the region. The Plan has resulted in the establishment of the African Medicines Regulatory Harmonization (AMRH) Programme. In response to a request from Member States, and building on prior collaboration between WHO and the East African Community in the regulation of ARVs, this led to the launch of the East African Community Medicines Registration Harmonization initiative in 2012. Regulatory control and the simplification of registration procedures are recognized as priority areas of work to increase ARV registration in African countries.

CHAPTER 4. THE ROLE OF INTELLECTUAL PROPERTY IN ACCESS TO ART

KEY MESSAGES

A number of important ARVs are still under patent protection. This limits the availability of cheaper generic versions in the countries concerned. Voluntary licences, in particular through the Medicines Patent Pool (MPP), are enhancing access to newer patented ARVs in a large number of LMICs. The main challenges now are in upper-middle-income countries (UMICs) – countries that still pay high prices – and in access to third-line medicines, new ARVs and pipeline products. Licence agreements have been negotiated for some of these products. While the geographical scope has expanded over the past years, particularly for licences negotiated by the MPP, many UMICs are not included in these agreements. However, in the recent agreement on dolutegravir (DTG), the MPP for the first time used public–private market segmentation and different levels of royalties to reflect different income levels of countries and therefore included more MICs. Countries that are not included in these licence agreements have to pursue other policy options to reduce costs, including the negotiation of reduced prices, and the use of Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities. Countries should also carefully assess the impact on public health before entering into trade agreements or, where applicable, World Trade Organization (WTO) accession agreements that contain measures that can delay the entry of generic competition. Overall, a balanced approach is needed that makes ARVs more affordable for LMICs, but also maintains incentives for companies to further invest in HIV/AIDS research, given the relatively small number of pharmaceutical companies that are still conducting research in this area.

The rationale for the patent system is to make investment in innovation attractive and to ensure that the knowledge contained in the patent application is accessible to society, so that it can be used. To achieve this aim, patents give the patent holder the right to exclude others from using the patented invention in exchange for disclosing the invention. In the area of medicines, patents keep generic copies off the market for the patent term.

While an increasing number of the older ARVs are today off patent, or nearing the end of their patent term, newer ARVs are still patent protected in many countries. This is the case for, inter alia, TDF, a number of second-line treatments, including ATV, RTV and lopinavir (LPV), and new or investigational ARVs, such as RAL, ETV, DTG, elvitegravir (EVG), rilpivirine (RPV), tenofovir alafenamide (TAF), and cobicistat (COBI) *(30).* In some cases there are also patents on specific forms or formulations of older ARVs, including patents on combinations that impact on the market for those specific forms/formulations (e.g. ABC/3TC, TDF/FTC).

Patents are territorial rights and thus the patent situation can vary from country to country. Originator companies do not always apply for patents in all countries, and when applied for, patents might not have been granted, or might have expired. In these cases competitors can market a generic product. They can also do so when a patent has been licensed to them, voluntarily or by the competent authority through a compulsory licence. Finally, they can market generic products when a patent holder declares that he or she will not enforce its patent rights (through a so-called "non-assert declaration"). However, patents are not the only intellectual property constraint generic manufactures need to deal with. In some markets their ability to market a product is also constrained by the protection of clinical test data through data exclusivity. This prevents generic manufacturers from relying on test data generated by the originator company to support their application for authorization to market a product for the period of data exclusivity. Members of the WTO are under certain conditions obliged to protect clinical test data against unfair commercial use and disclosure (Article 39.3 of the TRIPS Agreement), but not to provide data exclusivity. However, data exclusivity is often part of bilateral and regional trade agreements *(31).*

THE CURRENT PATENT SITUATION OF KEY ARVS

Because most patients are on first-line treatment, the patent status of TDF, 3TC, FTC and EFV is a key consideration. Gilead Sciences Inc. has given voluntary licences for the supply of generic TDF, and for FTC and combinations of TDF and FTC with other products, originally for 95 countries. Following negotiation with the MPP these licences were expanded to the MPP and their geographical patient coverage increased to 112 countries, including 100% of all patients in LICs, 96.1% of patients in LMICs, and 67% of patients in UMICs *(32).* Moreover, the agreement allows licensees to opt out of the TDF licence agreement and sell the product in all countries where the patents have not been granted, thus expanding further the countries that can benefit *(32).*

While the number of patients covered by these licensed ARVs increased, there are still countries with high HIV burdens, including Brazil (for combinations of TDF only), China and Mexico, which are not included in the MPP

licences and these countries continue to face high prices. In Brazil, this problem was mitigated by the fact that the patent on TDF was not granted but a patent was filed for the combination of TDF with FTC and EFV *(30).* Brazil now needs to use single drug formulations to administer the WHO-preferred regimen. With respect to EFV, after price negotiations failed in Brazil, they issued a compulsory licence to locally produce generic EFV. In China, the impact was mitigated through a differential pricing negotiation with the originator company.

Patents on EFV and 3TC have now expired in most countries. This has enabled the production of the two FDCs and three FDCs to administer the WHO preferred first-line regimens. As of 24 April 2014, six generic manufactures were WHO prequalified to supply [TDF + FTC + EFV] (six suppliers), [TDF + 3TC + EFV] (three suppliers), [TFD + FTC] (six suppliers) and [TDF + 3TC] (six suppliers).

For second-line treatment, access to AZT plus 3TC and to protease inhibitors (LPV or ATV, both with RTV) remains low. As the patents on the adult formulations of AZT and 3TC have expired in next to all countries, the patent status of LPV, ATV and RTV is a key consideration. LPV/RTV has limited patent protection in LICs and sub-Saharan Africa (with the notable exception of South Africa) and in addition its originator company, Abbvie, competes head-on in pricing with the four prequalified generic producers that also offer the product. Consequently, patents play no role in access to this product in LICs and sub-Saharan Africa. The situation is different in MICs, where Abbvie has patent rights. In the case of MICs, the adult formulation of LPV/RTV varied from US$ 619 to US$ 790 USD ppy. Finally, Ecuador, Indonesia and Thailand issued compulsory licences on LPV/RTV and can thus locally produce or import generic formulations.

Bristol Meyers Squibb (BMS) recently licensed ATV to the MPP for 110 countries, covering 88% of all patients worldwide *(34).* This will allow for generic competition in all LICs and in the majority of MICs. In addition, the licence allows generic manufacturers to offer the product for sale in countries where BMS does not have patent rights, expanding the pool of countries that can access generic versions of the drug to 144 *(35, 36).* This would still exclude 15 countries where BMS has patents on ATV, including Argentina, Brazil, Bulgaria, China, Egypt, Indonesia, Lebanon, Malaysia, Mexico, Peru, the Philippines, Romania, Thailand, Turkey and Ukraine *(36).* Those countries would need to agree on a preferential price, pursue a licensing agreement outside the MPP, or use TRIPS flexibilities to gain access to generic versions of the drug. Brazil seemingly already has such a licensing agreement in place.

In third-line treatment, access to DRV, RAL, and DTG are immediate concerns

Box 4.1 WTO Agreement on Trade-Related Aspects of Intellectual Property Rights

In January 1995, with the creation of the WTO, the Agreement on Trade-Related Aspects of Intellectual Property Rights (the TRIPS Agreement) introduced minimum standards for protecting and enforcing intellectual property rights. The Agreement raised the protection standards for a number of WTO members, in particular for those developing countries that previously did not grant product patents for certain technologies, namely in the pharmaceutical sector. Article 27.1 TRIPS thus requires WTO Members to make patents "available for any inventions, whether products or processes, in all fields of technology", including patents for pharmaceutical processes and products. The minimum term of protection that a country must make available under the TRIPS Agreement is 20 years from the filing date of a patent application.

Nevertheless, WTO Members under the Agreement retain important flexibilities, including the freedom to: exclude certain inventions from patentability; define patentability criteria; allow for parallel imports; introduce exceptions, such as early working for regulatory approval of generic products (Bolar provision) or experimental use exceptions; and determine the grounds for, and issue of, compulsory licences or to declare government use.

In 2001, WTO Member States, in view of the growing concern about the spread of HIV/AIDS and the high prices of ARV treatment, adopted the Doha Declaration on TRIPS and Public Health that reaffirmed the right of WTO Members to use these flexibilities. Under the TRIPS Agreement, least-developed countries benefit from a transition period that exempts them from granting and enforcing intellectual property rights, including the obligation to grant patents in general until 1 July 2021, provided that the WTO's non-discrimination principles are respected (WTO Document IP/C/64). An additional transition period runs until 2016, which exempts these countries from applying TRIPS provisions on the protection and enforcement of patents and undisclosed information specifically in the pharmaceutical sector *(39).* However, not all least-developed countries have made use of this transition period. For example, the African Intellectual Property Organization, which includes a number of least-developed countries, continues to grant patents on pharmaceutical products.

Licence agreements between the MPP and Gilead make it possible to supply generic versions of COBI to 103 countries, and of EVG and the Quad (combination of TDF, FTC, COBI and EVG) to 100 countries. Nine additional countries will be able to procure these medicines through the bilateral semi-exclusive licences granted by Gilead to certain generic companies. The agreements Tibotec/Janssen signed for RPV cover 112 countries. Licences between the MPP and ViiV Healthcare on paediatric abacavir (ABC) include 118 countries, accounting for 98.7% of children living with HIV needing treatment. The licence for DTG for paediatric and adult use includes countries accounting for 93.4% of people living with HIV and over 99% of children living with HIV *(37).* In the agreement on DTG, the MPP for the first time used different levels of royalties to reflect different income levels of countries, which allowed inclusion of six MICs (Egypt, India, Indonesia, the Philippines, Turkmenistan and Viet Nam). Merck has entered into two licence agreements with generic companies for RAL. However, the number of licensees and the territory are very limited and only include sub-Saharan Africa and other LICs. So far no prequalified generic versions of RAL are available *(26).*

While the voluntary licence agreements mentioned do not solve the access problems of all countries, they are having a significant impact in sub-Saharan Africa and LMIC. Other mitigating mechanisms such as the negotiation of preferential prices can be used, although they are less effective than generic competition. Finally, when countries and companies cannot agree on affordable prices, governments can also resort to using compulsory licensing. The WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property urges governments to "consider", whenever necessary, adapting national legislation in order to use to the full the flexibilities contained in the TRIPS Agreement (Box 4.1), including those recognized by the Doha Declaration on the TRIPS Agreement and Public Health and the WTO decision of 30 August 2003.

POLICY OPTIONS TO INCREASE ACCESS TO ARVS

Voluntary licensing

As previously discussed, for an increasing number of patented ARVs, patent holders have signed voluntary licence agreements that allow for the production and marketing of generic ARVs in defined territories. Because this makes the ARVs available to the great majority of people living with HIV globally, voluntary licencing has emerged as the key approach to manage the intellectual property rights on ARVs. The agreements differ in the extent to which MICs are included. As not all MICs are included, the MPP and originator companies should explore options to include more MICs in the scope of their agreements. Unlike the licences negotiated through the MPP (Box 4.2), the terms of the agreements of licences awarded bilaterally from the originator companies to generic companies have not been disclosed publicly. This limits the ability to compare and provide comments on them.[1]

Box 4.2 Voluntary licensing and the MPP

Established in 2010 with support from UNITAID, the MPP seeks to address the need for access to new, patented HIV medicines in developing countries through collaboration with patent holders. The MPP operates by negotiating public health-oriented voluntary licences to enable the development of quality-assured generic medicines for use in LMICs. The MPP aims to promote market competition, ultimately to drive down prices and make medicines more accessible. The MPP also seeks to facilitate the development of new paediatric and fixed-dose formulations.

Since its creation, the MPP has concluded licence agreements on eight ARVs, including WHO-recommended first- and second-line treatments in adults and children, and the MPP's generic partners have supplied over 1 billion doses of medicines in LIMCs. The full text of the MPP licences is made public in an unprecedented effort to ensure transparency of licensing terms. For more information see www.medicinespatentpool.org.

Compulsory licences

For those ARVs that are not included in the current voluntary licence agreements, or for countries that are not covered by these agreements, another option to address public health needs under the TRIPS Agreement is to issue a compulsory licence or to declare government use. Both instruments permit the use of the patented invention without the authorization of the patent holder. Article 31 of the TRIPS Agreement contains certain conditions, including that those who seek a compulsory licence must first try to obtain a voluntary licence, except in cases of a national emergency, public non-commercial use, or when remedying a practice judged as anticompetitive *(31).*

1 A list of all licence agreements in the area of HIV is available in reference *(33).*

Table 4.1 highlights that a number of countries have used compulsory licences to increase access to medicines. While in the beginning African countries were using the instrument, more MICs such as Brazil, Ecuador, Indonesia and Thailand have issued compulsory licences in recent years.

Under a compulsory licence, countries can either import or locally produce the medicine. However, local production requires appropriate technical knowledge and production capacity as well as access to a reliable source of active ingredients, unless these are also locally produced. This can be challenging, as illustrated by the fact that it took Brazil two years to locally produce EFV under a compulsory licence *(31)*.

Export of medicines produced under compulsory licence is restricted by Article 31 of the TRIPS Agreement, which requires that production be "predominantly for the supply of the domestic market". This limits the possibility of imports under a compulsory licence for countries that cannot produce the needed medicines and also limits

Table 4.1 Compulsory licences for ARVs

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; DDI; EFV; LPV/r; TDF; TDF+FTC; TDF+FTC+EFV
2012	Ecuador	GU	UMIC	Local production	5 of US price[b]	ABC/3TC

CL, compulsory licence; GU, government use; HIC, high-income country; INN, international non-proprietary name; NA, not available.

[a] Issued under so-called WTO paragraph 6 system for export to Rwanda.

[b] 5% of United States price adjusted by difference in gross domestic product.

Source: WHO *(33)*.

possible economies of scale, especially in countries where the home market is small. To address this potential difficulty, WTO Members adopted a mechanism that waives this restrictive condition applying to standard compulsory licences in certain circumstances. This mechanism, often referred to as the "Paragraph 6 System", provides WTO Members with an additional flexibility under which they can grant special compulsory licences for the purpose of allowing the manufacturing of pharmaceutical products exclusively for export to countries in need of those products subject to certain terms and conditions *(31, 40).*

Overall, the number of compulsory licences has been limited, but their use has greatly increased the pressure on patent holders to seek more consensual solutions in developing countries. Also the mere threat to use the option to grant compulsory licences increases their bargaining power in price negotiations with originator companies.

Differential pricing

Another potential option to reduce costs is differential pricing. Under the concept of differential (or tiered) pricing, a dominant market player uses a form of price differentiation based on a country's willingness or ability to pay for the product, as opposed to uniform pricing. Such price differentiation is feasible if the company is able to effectively segment markets to prevent the diversion of products from the lower-price to the higher-price market *(31).* In ARVs, companies typically provided three tiers: one for low price for LICs, low development index and sub-Saharan Africa; differential prices "to be negotiated" for MICs; and a third tier for high-income countries. As in the area of licence agreements, the UMICs are the main challenge. While companies may be willing to forego profits in poor countries with a high disease burden, they expect higher returns in UMICs.

Managing patentability standards

While the WTO TRIPS Agreement has introduced minimum standards, it leaves it to WTO Members to further define and interpret the patentability standards. Thus, a medicine can be patented in one country and not in others. For example, the patent on TDF was rejected in Brazil and India and was granted in China and Mexico.

Because medicines are usually not protected by one patent, but several relating to different aspects of the product, some countries, including Argentina, India and the Philippines, have adopted narrow patentability criteria or excluded certain pharmaceutical inventions from patentability. In India, for example, new forms of a previously known chemical compound, such as salts or polymorphs, or new dosage forms are not considered an invention, unless they result in the enhancement of the known efficacy of that substance. In the past few years, based on this rule, the Indian Controller of Patents has rejected a number of patents, including in 2008 and 2009 for the paediatric suspension of NVP hemihydrate and TDF *(31).*

Enabling pre-and post-grant opposition

The rejection of patent applications or the revocation of patents that do not fulfil the patentability criteria often go back to oppositions filed by competitors or nongovernmental organizations. In many national or regional patent systems, third parties can file oppositions against a patent either before or after its grant (pre- or post-grant opposition). Examples with respect to ARVs include patent applications for a number of ARVs that were rejected or withdrawn, in India based on pre-grant oppositions, including applications for LPV/r, TDF and ABC *(44, 38).*

CHALLENGES IN THE SHORT TO MEDIUM TERM

Legal situation in India

Many of the current ARVs are produced as generic versions in India. This is because India only allowed for the filing of product patents for pharmaceuticals from 1995 and most of these first-line or some second-line ARVs were not novel by that date. India also benefited from a specific transition period under the TRIPS Agreement that allowed it to delay the introduction of patents on pharmaceutical products to 2005. Since then, India has been obliged to grant pharmaceutical product patents. Although India limited the patentability of certain pharmaceuticals through Section 3d of the Indian Patent Act, the number of key products that will be patented in India will increase and therefore prevent generic manufacturers from bringing their products to the market, unless they are included in future licence agreements.

Free trade agreements

Some bilateral and regional trade agreements include standards of protection for intellectual property that increase protection of intellectual property and limit the use of the policy options and flexibilities that WTO Members have under the TRIPS Agreement *(31, 41).* In this context, the UN Political Declaration on HIV/AIDS calls upon UN Members "[to] ensure that intellectual property rights provisions in trade agreements do not undermine

these existing flexibilities, as confirmed by the Doha Declaration on the TRIPS Agreement and Public Health".

In this respect, the WHO Global Strategy and Plan of Action urges Member States to "promote active and effective participation of health representatives in intellectual property-related negotiations, where appropriate, in order that such negotiations also reflect public health needs" and "take into account, where appropriate, the impact on public health when considering adopting or implementing more extensive intellectual property protection than is required by the Agreement on Trade-Related Aspects of Intellectual Property Rights, without prejudice to the sovereign rights of Member States".

CHAPTER 5. COPING WITH INCREASING GLOBAL DEMAND FOR ARVS

KEY MESSAGES

The WHO/UNAIDS ARV demand forecasting working group predicted that by the end of 2016 there will be 16.8 million people on ART. Satisfying this demand will require more production capacity for their APIs. Right now, there are supply constraints for zidovudine (ZDV) and in the near future, supply constraints for lamivudine (3TC) might become a problem. This requires that the market for ARVs in LMICs remains economically viable. This requires that the risks for manufacturers to operate in the ARV market be minimized, which can be achieved by limiting regulatory hurdles; early intelligence sharing on forecasts of ARV demand; improving tender and procurement practices, including timely payment of suppliers; and abandoning the "winner takes all" approach in public tender. However, the challenge of dealing with rapidly increasing demand for ARVs is also a great opportunity for the manufacturers: they saw the value of the LMIC ARV market multiply more than 13-fold in less than 10 years. The number of manufactures with WHO prequalification or US FDA approval for at least one ARV increased from 13 in 2004 to 18 in 2013. However, the market is also concentrating in the hands of a few major players, both on the suppliers' and the buyers' side. This might cause problems for supply security and become a threat for competition in the future. Managing these threats will require close attention from the main buyers of ARVs in the near future.

DEMAND FOR ARVS SET TO INCREASE BY 70% IN THE NEXT THREE YEARS

Following their commitment to reach 15 million people on ART by 2015, and spurred on by the revision of the WHO guidelines on ART that increased the number of people eligible for ART to 28.6 million, countries have continued to increase their investment in ART access in the past decade.

To help ensure that the producers are ready to supply the increasing quantities of ARVs needed for the scale-up, WHO, in collaboration with UNAIDS, convened a global Forecasting Technical Working Group, comprising Clinton Health Access Initiative (CHAI), United Nations Children's Fund (UNICEF), GFATM, PEPFAR and the Futures Institute. The group develops yearly forecasts of how much and which ARV will be needed in the next three years. The total number of people on treatment is estimated using three scenarios:

- extrapolating the number of people in ART from the annual WHO/UNAIDS/UNICEF reports on universal access to HIV prevention, treatment, care and support;
- extrapolating the targets stated by countries for their future treatment access;
- extrapolating the data on treatment access from 21 high-burden countries compiled by CHAI.

The results of the three scenarios are used and averaged arithmetically to generate the projected global ARV demand. The proportion of people using each of the ARVs recommended in the WHO ART guidelines is estimated, using extrapolation of past use from the WHO ARV surveys and of past and planned use from in-country quantification in the 21 countries supported by CHAI. The estimates are validated with procurement trends in GPRM, in PEPFAR procurement, and procurement by the GFATM through the voluntary pooled procurement mechanism. The forecasted demand for 2013 up to the end of 2016 is presented in Figure 5.1. These data suggest that by the end of 2016 there will be 16.8 million people using ART (range 15.7–18.5 million). This represents a nearly 70% growth of the demand over a 3-year period *(45, 46)*.

MANAGING INCREASED DEMAND

In the 2012 WHO/UNAIDS ARV manufacturers meeting *(45),* the manufacturers of finished formulations indicated having sufficient formulation capacity to cope with 20 million people on ART. Therefore, coping with rapidly increasing demand is a challenge mainly for the manufacturers of APIs. Some overcapacity in API production is needed to avoid global supply shortages. From the comparison of the anticipated future demand for different ARVs with the production capacity of APIs reported to WHO in 2013 (Figures 5.2 and 5.3), it is obvious that new API production capacity will be needed, across the board, for all ARVs by 2017.

While caution is needed with the estimate of demand for individual ARVs, production capacity installed for TDF and EFV is likely sufficient to satisfy demand in the near future. This concurs with the 2014 landscape report on HIV medicines by UNITAID *(47).* Under-reporting of installed API production capacity likely explains why the production capacity for LPV and RTV is shown in Figure 5.3 as unable to satisfy current demand. However, the supply capacity for ZDV and 3TC might come under pressure soon. UNITAID estimates that the additional API production

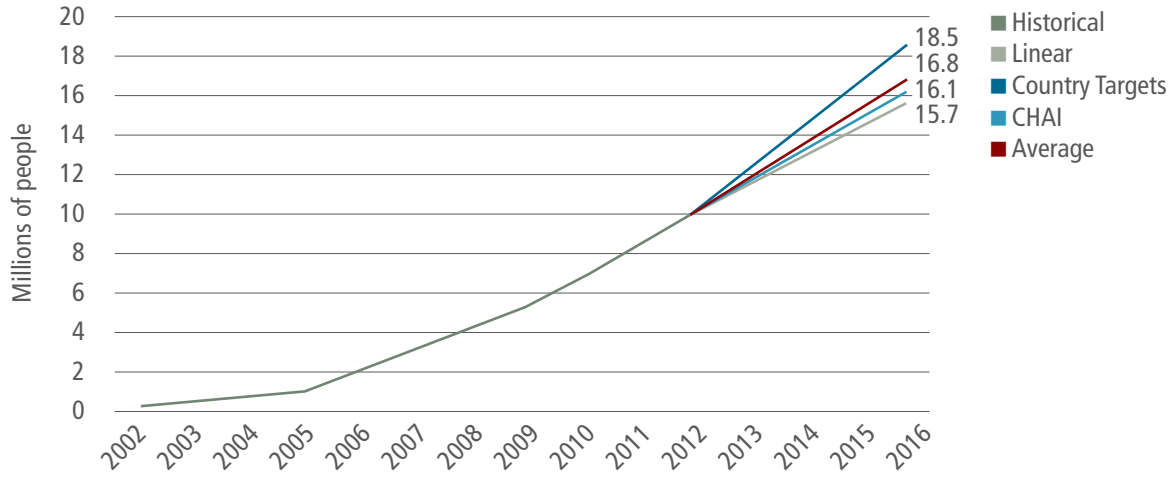
capacity is likely to emerge by new suppliers entering the quality assured market, but this begs the question whether producing them will be economically viable.

ON-GOING THREATS AND HOW TO MANAGE THEM

According to the manufacturers of ARVs, the viability of the ARV market in LMICs is under threat because of difficult market entry, long prequalification times, limited access to reliable forecasting information, and the cost of APIs *(43)*. The manufacturers urged that serious attention be paid to improving procurement practices, including abandoning the "winner takes all" approach in public tender, timely payment of suppliers, limiting regulatory hurdles, and early intelligence sharing. However, others also asserted that the lack of transparency on the true cost of production precluded their accepting the assertion that profit in the ARV market is presently insufficient to secure supply security *(43)*.

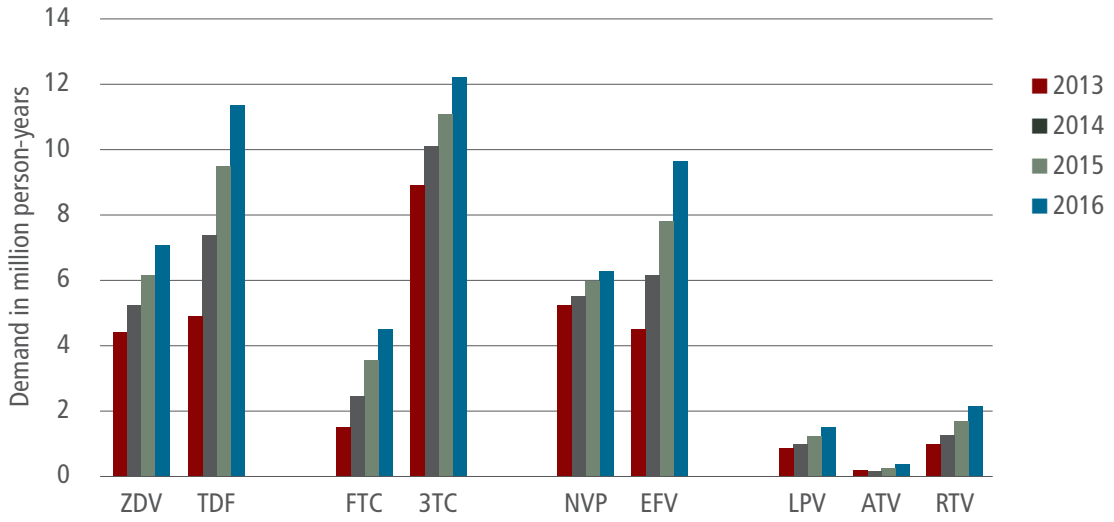
In addition, it is a great opportunity for the manufacturers that the volume and value of the LMIC ARV market has continued to increase. As shown in Figure 5.4, in 2004 the GPRM registered US$ 73 million of sales. By 2009, this had increased to US$ 742 million and in 2012 to US$ 987 million – a greater than 13-fold increase in less than 10 years. The manufacturers have capitalized on this increased opportunity: the number of manufacturers with a WHO prequalification or a stringent regulatory approval for at least one ARV increased from 13 in 2004 to 19 in 2012. With the exception of Varichem Pharmaceutical (Pvt) Ltd – a small manufacturer operating from Zimbabwe – all WHO-prequalified manufacturers remained on record in GPRM as supplying ARVs to LMICs in 2013 and 2014. At the same time, the LMIC market has been concentrating in the hands of a few dominant players: Figure 5.4 illustrates that Mylan (Matrix Laboratories Ltd), Hetero Drugs Ltd and Aurobindo Pharma Ltd became the major players, with Cipla Ltd Ranbaxy Laboratories Ltd, Strides Arcolab and Abbott (now Abbvie) in second tier, and other companies remaining relatively small – some with decreasing value of their sales. Concentration on the side of the producers might carry a risk for supply security when a major producer drops out, and for the competitiveness of this market when smaller producers are driven out. Managing this risk will require close attention from the major buyers of ARVs for LMICs. On the side of the larger buyers, PEPFAR and GFATM are emerging as the major players. The new procurement approach of GFATM for ARVs that is due to be launched in July 2014 aims, in addition to achieving competitive pricing, to improve on-time delivery and strengthen the sustainability of the ARV market.

Figure 5.1 Projected numbers of patients on ART based on country target, linear and CHAI projections, 2002–2016



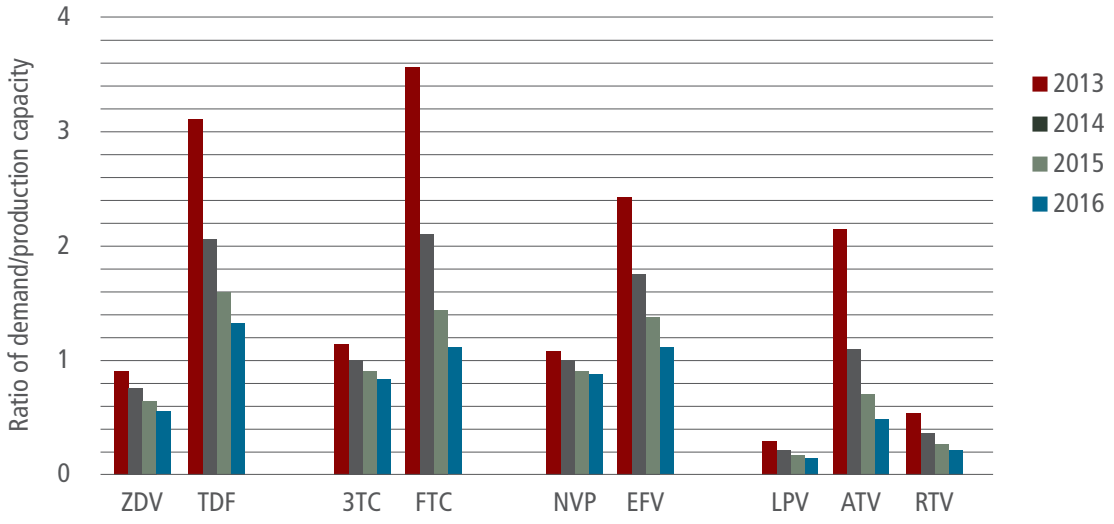
Source: WHO *(46)*.

Figure 5.2 Projected numbers of patients using different ARVs, 2013–2016



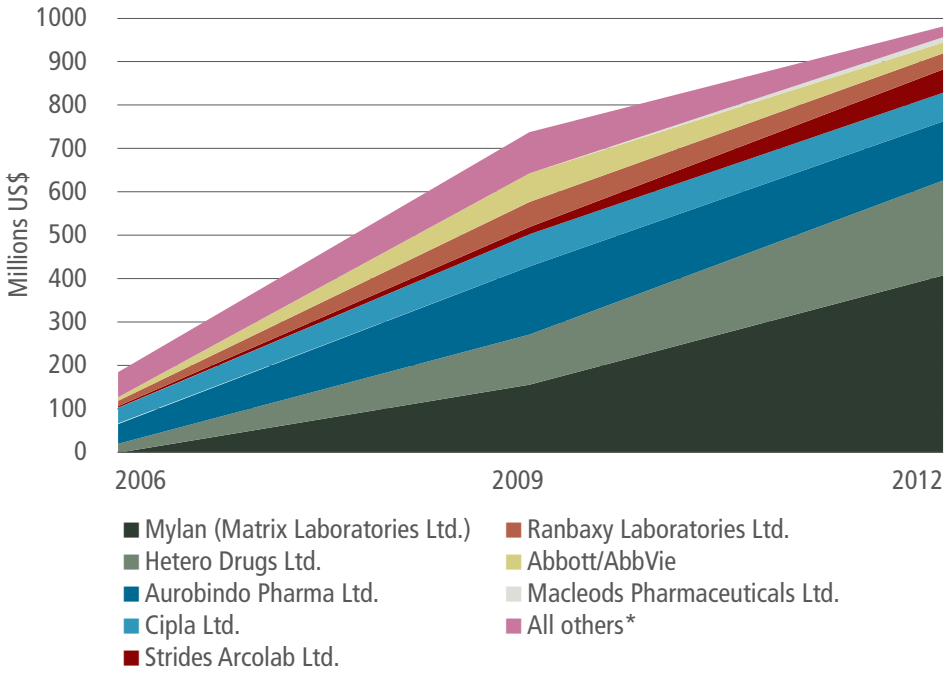
Source: WHO *(46)*.

Figure 5.3 Ratio of demand for ARVs over reported API production capacity in 2013



Source: WHO *(6, 46)*.

Figure 5.4 ARV suppliers and value of their sales (in Millions US$) registered in GPRM, 2006–2012



*Includes Gilead Sciences, Inc., GlaxoSmithKline Ltd. (ViiV), Aspen Pharmacare Ltd., Emcure Pharmaceuticals Ltd., F. Hoffmann-La Roche Ltd., Merck, Sharp & Dohme Ltd., Varichem Pharmaceuticals (PVT) Ltd., Janssen-Cilag S.p.A. & Tibotec, Boehringer Ingelheim, Bristol-Myers Squibb, and Micro Labs Ltd.

Source: GPRM database.

CHAPTER 6. STRENGTHENING PHARMACEUTICAL SUPPLY MANAGEMENT SYSTEMS

KEY MESSAGES

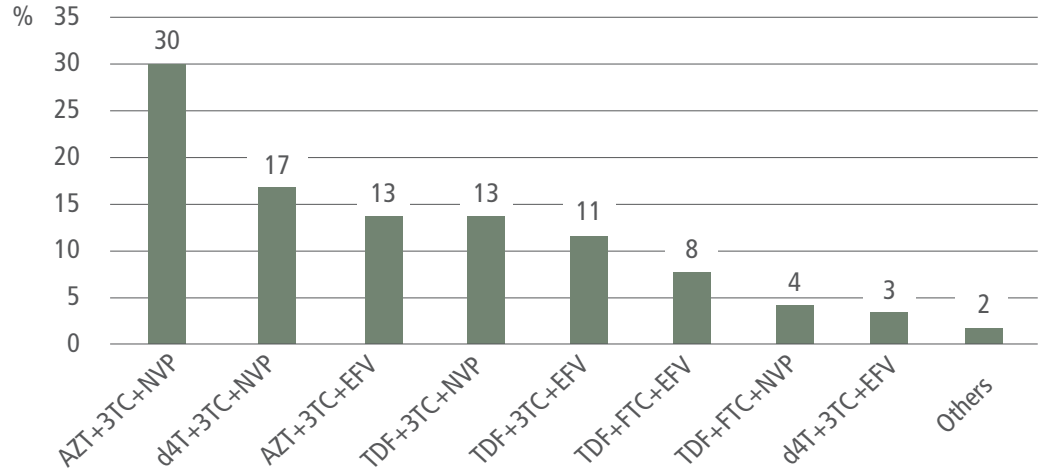
Ensuring that ARVs are always in stock can only be achieved if the national pharmaceutical supply management system functions without fail at all levels of the health system. Numerous countries have yet to update their treatment programmes to bring them in line with the 2013 WHO consolidated guidelines, which, in addition to changes in the treatment initiation criteria, often also require changing the treatment regimens used. To help countries manage this transition, WHO published a policy technical brief in March 2014 with detailed operational considerations on how to deal with the supply management challenges. Beyond changing the treatment regimens, many treatment programmes continue to battle stock-out threats. The Coordinated Procurement Planning (CPP) Initiative, which monitors the supply situation for ARVs in 22 countries, consistently has around half of its client countries on red alert for imminent stock out. It should therefore come as no surprise that in recent years between 30% and 45% of LMICs annually reported having stock outs. Better supply planning and securing timely funding for essential supplies are the two top priority actions that procurement and supply management (PSM) managers need to pursue to prevent stock outs. Long-term actions should focus on strengthening the logistics management information systems and human resource capacity-building in PSM, including monitoring and evaluation of the national supply system. Countries should consider using the opportunities offered by funding for HIV to strengthen their supply systems more broadly. This provides a great opportunity to increase the impact of investment in HIV for the health of entire populations.

PREVENTING ARV REGIMENS ANARCHY

Data from the 2013 WHO ARV survey *(10)* show that across 69 responding countries 101 different adult first-line ARV regimens and 45 paediatric first-line ART regimens were in use, some containing obsolete medicines. The median number of regimens used by adults was 8 (IQR 6–14), and remained stable during the past 5 years *(7–10)*. However, even while this means that about half of all countries use a limited number of treatment regimens and put in significant efforts to contain therapeutic anarchy, it also documents that other countries still have a long way to go towards the rationalization of their treatment approaches.

Bearing in mind that the 2013 survey reports on the use of ARVs in 2012, and that since then the use of d4T has decreased considerably, Figure 6.1 shows the most frequently used treatment regimens in 2012. It illustrates that leaving the choice of treatment regimens wide open introduces a huge management challenge. A total of 98% of patients are covered by eight first-line ART regimens, while 2% of patients are covered by the remaining 93 ARV regimens. This represents a high number of regimens where one to two regimens would have been sufficient.

Figure 6.1 First-line regimens used by adults and adolescents (n = 4.9 million), end 2012*



*d4T use reported here is d4T use in 2012. Since 2012, d4T procurement, which reflects the use in the subsequent year , has decreased significantly to 2% in 2013.
Source: WHO survey on ARV use, 2013 *(10)*.

Managing the continuous availability of all drugs for an additional 98 different regimens is a significant challenge and creates market segmentation of the supply system, stock outs, and more frequent expiry of unused drugs.

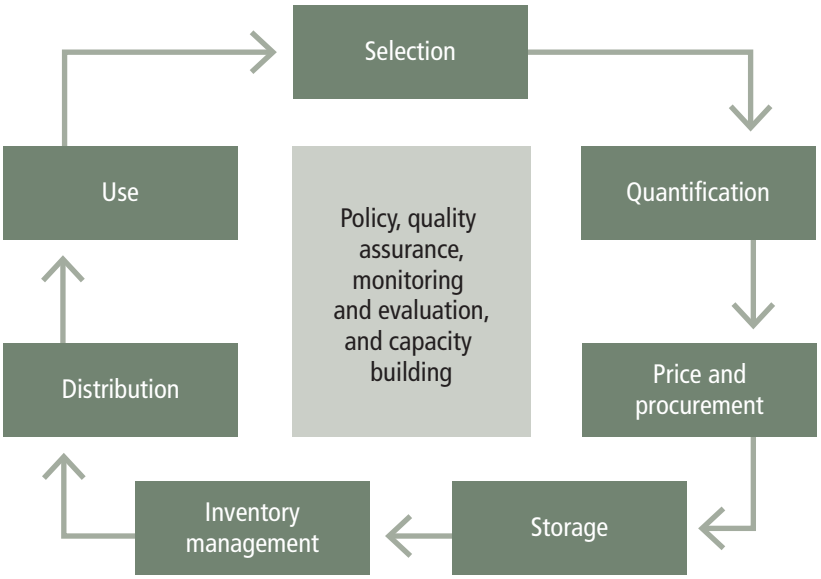
PREVENTING DRUG STOCK OUT AND EXPIRY

As ART cannot be interrupted without risk for the development of drug resistance – and hence worse survival – people on ART need an uninterrupted supply of ARVs. As shown in Figure 6.2, PSM systems need to carry out a variety of activities at all levels of the health care delivery system, from the national programme level down to facilities where medicines are dispensed to patients. The framework emphasizes the cyclic relationships between selection, procurement, distribution and use activities, all of which are enabled by a strong management support system *(48).* Stock out and drug expiry can only be prevented and full supply guaranteed when all parts of the PSM system in the framework cycle function without fail at all levels of the health system. In addition, they need to be flexible so that they can adapt to the changing treatment recommendations, which are regularly updated.

Unfortunately, PSM systems in LMICs are often underdeveloped and therefore coping with the risk of stock out is a daily concern for front-line staff. Data to quantify the stock-out risks for ARVs are available from the Coordinated Procurement Planning (CPP) Initiative, a collaborative venture between CHAI, GFATM, PEPFAR/Supply Chain Management System (SCMS), UNAIDS, UNITAID, United States Agency for International Development (USAID), UNICEF, WHO and other stakeholders. The CPP Initiative currently monitors stock-out risks in 22 countries and classifies their stock-out risks into three risk levels *(49).* The 22 countries are: Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Cote d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Guinea, Mali, Mozambique, Nigeria, South Sudan, Swaziland, United Republic of Tanzania, Uganda, Zambia and Zimbabwe. Figure 6.3 shows that in the first quarter of 2014 half of those countries were at high risk of stock out – a situation fairly representative of the picture seen globally in the past few years.

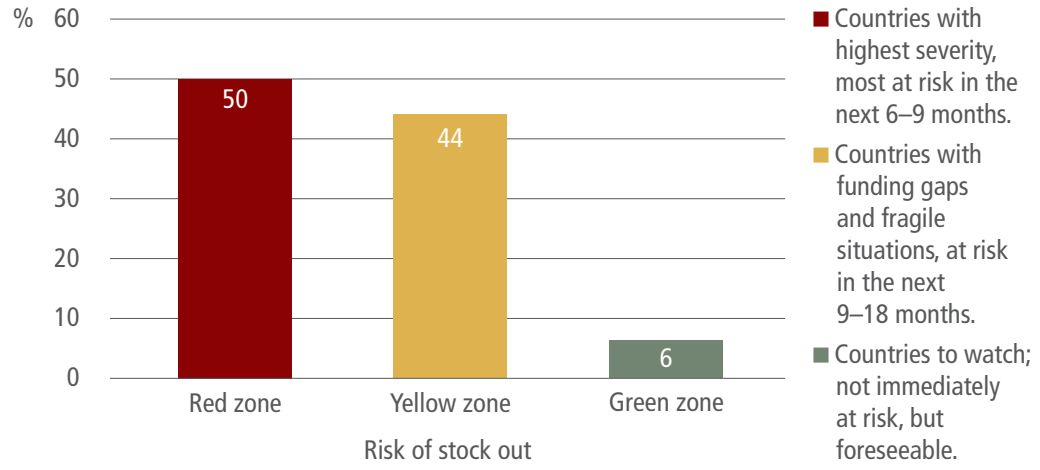
As illustrated in Figure 6.4, it should be no surprise that in the past few years stock out rates at facility level were variously reported as between 30% and 45% annually *(11-15, 1)*. Moreover, measuring the stock-out rate of ART gives an optimistic assessment of the ability to supply HIV/AIDS patients and the population in LMICs with the other essential medicines that they need to deal with their health problems: the UN Millennium Development Goal Gap Task Force report 2012 found that in LMICs only 50.1% of the public sector and 67% of the private sector public health facilities had available a representative selection of essential medicines *(50, 51)*.

Figure 6.2 PSM cycle



Source: WHO *(48)*.

Figure 6.3 Percentage of CPP-monitored countries (n = 22) by risk of stock out, first quarter of 2014



Source: CPP *(49)*.

In their attempts to secure access to ARVs, countries employ numerous emergency measures to avoid treatment interruption, including *(1)* :

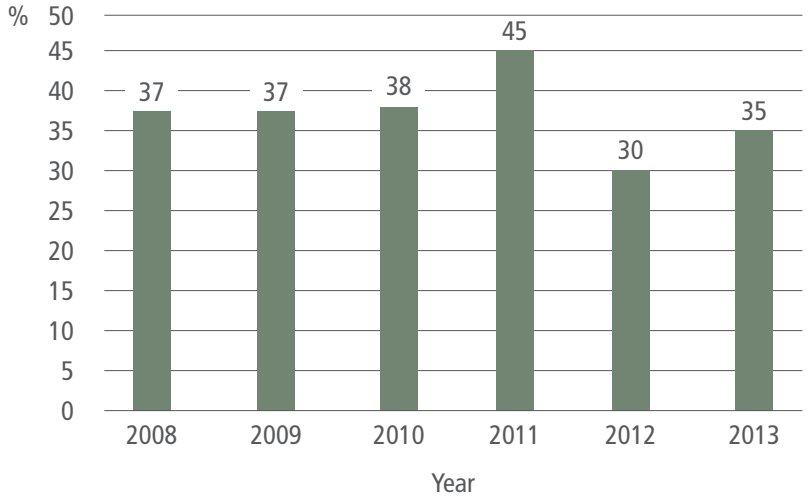
1. Switching patients to other ART regimens with the intent of switching back to the original regimen once the stock-out situation abates. This is poorly implemented in most cases.
2. Transferring ART from neighbouring health facilities, regions or even countries to ensure continuous treatment.
3. Procuring emergency supplies, using emergency funding. UNITAID supplied emergency funds for paediatric and second-line treatments to 21 countries facing stock outs in 2012. In 2013, five countries received support from PEPFAR's Emergency Commodity Fund for a total of US$ 13 million.

However, those are stop-gap measures that should not be taken as a substitute for sustainable strengthening of the PSM system. The key has been to create efficient pharmaceutical and commodity management systems that will be sustained for years to come, with the outcome being a stronger pharmaceutical sector that serves not only specific HIV/AIDS-related needs, but all health needs *(52)*.

While wholesale PSM systems overhaul should remain a goal, it is necessary to focus in the meantime on the main causes for supply interruptions. The two major causes are poor procurement planning and financial insecurity. Training teams responsible for PSM in ART sites, provincial stores and central medical stores in using the 12 PSM indicators proposed by WHO and its PSM partners – including the six early warning indicators for stock out *(48)*, and creating a monthly reporting mechanism to track supplies, proved useful to improve supply management in several countries *(53, 54)*. Tracking finances and finance processes to ensure timely funding is another key responsibility for PSM managers, as it enables timely communication of needs to the government and donors involved in the ART programme.

Longer term, higher intensity activities would include overhauling logistics management information systems, including moving them from paper-based to electronic systems, and strengthening the human resource base for PSM systems. Countries such as Zimbabwe have leveraged HIV funding to deploy a variety of innovative uses of mobile technology to improve the logistics management information system for ART and other health commodities *(55–62)*. To increase on-time reporting rates from ART sites, facility staff fill out their paper logistics forms manually, and then take photographs of the completed forms with a camera phone. Images of the forms are sent directly to the logistics unit at the central level, where the information is entered into a central database and used for decision-making. The People that Deliver initiative is a recent global partnership dedicated to building global and national capacity to plan, finance, develop, support and retain the national workforces needed for the effective, efficient and sustainable management of health supply chains in both the public and private sectors. The People that Deliver initiative works closely with the International Association of Public Health Logisticians that facilitates networking and south-to-south exchange to improve the performance of supply chain and logistic information systems of ARVs and other health commodities.

Figure 6.4 Percentage of LMICs that reported ARV stock outs, 2008–2013



Source: WHO, UNICEF, UNAIDS *(11–15, 1)*.

Countries should consider using the opportunities offered by funding for HIV, and the emergence of recent capacity-building initiatives, to strengthen their supply systems more broadly *(63–64)*. This is because in addition to ARVs, HIV/AIDS patients also need access to other essential medicines. Box 6.1 highlights that strengthening PSM systems also provides a great opportunity to increase the impact of investment in HIV for the health of entire populations.

Box 6.1 Examples of country-level Success: Uganda and Namibia

Uganda's Ministry of Health is integrating the health commodity supply chains, starting with bringing HIV commodities into the essential medicines supply *(60)*. As a result of this integration, a web-based system for ordering ARVs has facilitated integration and streamlined ordering and reporting of ART commodities through the Ministry's centralized health management information system. Launched in 2010, the Quantification Procurement and Planning Unit within Uganda's Ministry of Health focuses on the coordination, standardization, harmonization, streamlining and centralization of all central-level activities related to planning for essential medicines and health supplies.

In Namibia, the human resource issue for PSM was tackled successfully in 2005. An assessment of the Namibian pharmaceutical sector followed by concrete recommendations was the first step in identifying and implementing both short-term and long-term solutions to the pharmaceutical personnel shortage *(61)*. As an immediate solution, the Ministry of *Health* increased the number of qualified pharmaceutical staff in public service by identifying vacancies and delineating needed responsibilities. A Namibian human resource firm recruited and hired new staff to fill government vacancies, while USAID provided financial support. The initiative doubled the number of government pharmaceutical staff, and eventually the Ministry of Health absorbed them into the public sector *(62)*. This collaboration created a new mechanism to help the government quickly fill urgent personnel needs in the public pharmaceutical sector, while allowing it to gradually absorb the positions into its existing structure.

CHAPTER 7. CONCLUSIONS

While the increase in treatment access in the last decade was a significant accomplishment and represents a landmark success in the history of global health, there are still many challenges ahead. There were more than 11.7 million people in low- and middle income countries receiving treatment at the end of 2013, but with the new treatment guidelines, WHO estimates that 28.6 million people need ART. Clearly, treating all these people in need of ART is not going to happen unless ART becomes even more affordable than it is now. This will likely be possible. Data from this report show that in the past decade the price of individual ARV formulations has decreased. Further price decrease will likely be possible with dose reduction and treatment optimization strategies.

A second area in which we will likely see change is the uptake of second-line and third- line treatment. In WHO's 2013 consolidated guidelines on the use of ART *(3),* WHO recommended that ART be monitored with the assessment of VL. Countries such as Kenya and Uganda have been rolling out increasing access to VL testing in central laboratories, using dried blood spots instead of plasma to collect blood samples for testing. The future availability of point-of-care tests to assess VL will also make it easier to detect treatment failures. It is therefore expected that the demand for and uptake of second-line and third-line ART will increase.

While significant price decrease occurred in WHO recommended first line regimens, the cost of second-line and third-line treatment remains an issue. However, with licensing and increasing volumes, the cost of these treatments will likely decrease, because they will become more attractive to generic manufacturers. This requires that the newer medicines will be licensed to generic manufacturers at the same rate as is now the case, and that the geographical scope of voluntary licences be expanded. The latter should also be possible; for example, when the internal market of MICs can be segmented into high-volume/low-cost and low-volume/high-cost segments. The alternative would be for countries facing high prices to consider other options, such as price negotiations and the use of WTO TRIPS flexibilities. Overall, a balanced approach is needed to ensure ARV affordability for all countries, and to maintain incentives for companies to further invest in HIV/AIDS research and development.

With increased consolidation around WHO-recommended treatment regimens, the future outlook for market viability for ARVs is strong. According to our forecasts, the ARV market is set to grow by 70% in the next three years. Strategies to sustain growth will include continued focus on simplified treatment regimens. This will decrease the proliferation of irrational treatments and enable the economies of scale needed to produce the APIs at low cost. It is presently the mainstay of WHO's strategy to increase access to paediatric treatment, access to which is lagging behind that of adults, with paediatric ARVs representing less than 7% of the ART market in LMICs. Other strategies are: to increase transparency about future demand; in procurement, to split orders between several suppliers, so that the existing high-quality manufacturers stay in the market; prompt payment of drugs when they are delivered (or even prepayment); and alleviating regulatory hurdles.

However, the need to have an efficient regulatory approval process without undue hurdles should not be taken to mean that regulatory oversight can become less. We found that at present major parts of the ARV market in LMICs are quality controlled through ad hoc mechanisms. If perpetuated, this represents a risk to both manufacturers and patients using these medicines. The long-term objective should be for countries to strengthen their NMRA capacity and work towards incorporating international standards for quality control and assurance. Shorter-term options to ensure access to safe, effective quality products include the adoption of WHO prequalification or US FDA tentative approval status to support national regulatory approvals, and waiver of regulatory fees for products with WHO prequalification for a time-limited period after registration. WHO is working with country regulators to improve technical capacity and harmonize regulatory standards and practices.

Finally, supply management and distribution of ARVs remains the weakest link in ART programmes. With universal coverage of ART globally now a key objective, the decision-makers and advocates for ART must realize that they cannot continue to ignore the need to strengthen the supply chains required to deliver the products and services. We can no longer continue with a situation whereby half of LMICs being monitored by the CPP Initiative are on red alert for imminent stock out of ART, as was the case in early 2014. Urgent investment in the upgrade of supply management and distribution systems is needed to tackle this threat. These initiatives should address not only ARV and diagnostics shortfalls, but also all essential drugs and diagnostics.

Some regions have now begun to report on access and use of ARV medicines *(65)*. WHO encourages more regions to move in this direction and share their reports with other stakeholders. WHO will continue to provide normative guidance on the use of ARVs to support their rational and effective use, and to work towards increased transparency of the LMIC ARV market through the production of annual global ARV demand forecasts. It will continue to collect strategic information on the use of ARVs through surveys and GPRM, API and regulatory databases. In addition, WHO will continue to support the availability of high-quality ARVs through its prequalification programme, and to support simplification of the drug regulatory processes to ensure the safety of ARVs for all patients.

REFERENCES

1. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. 2014 global update on the health sector response to HIV. Geneva: World Health Organization; 2014.
2. UN General Assembly, 65th Session, A/RES/65/277: Political Declaration on HIV/AIDS: Intensifying our Efforts to Eliminate HIV/AIDS. Resolution adopted by the General Assembly on 10 June 2011 (Article 66).
3. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en,accessed 30 June 2014).
4. Global Price Reporting Mechanism for HIV, tuberculosis and malaria [website]. Geneva: World Health Organization (http://www.who.int/hiv/amds/gprm/en, accessed 30 June 2014).
5. HIV/AIDS. Drug regulatory status database [website]. Geneva: World Health Organization (http://www.who.int/hiv/amds/patents_registration/en, accessed 30 June 2014).
6. Sources, quality and prices of active pharmaceutical ingredients of antiretroviral drugs. Results of 2012 survey. Geneva: World Health Organization; 2012 (http://www.who.int/hiv/pub/amds/api2012/en, accessed 30 June 2014).
7. WHO Global Survey on ARV use in 2010. Results reported and used in the annual global forecasts of global ARV demand.
8. WHO Global Survey on ARV use in 2011. Results reported and used in the annual global forecasts of global ARV demand.
9. WHO Global Survey on ARV use in 2012. Results reported and used in the annual global forecasts of global ARV demand.
10. WHO Global Survey on ARV use in 2013. Results reported and used in the annual global forecasts of global ARV demand.
11. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report 2008. Geneva: World Health Organization; 2008.
12. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report 2009. Geneva: World Health Organization; 2009.
13. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report 2010. Geneva: World Health Organization; 2010.
14. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report 2011. Geneva: World Health Organization; 2011.
15. World Health Organization, United Nations Children's Fund, Joint United Nations Programme on HIV/AIDS. Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report 2012. Geneva: World Health Organization; 2012.
16. World Health Organization, United States President's Emergency Plan for AIDS Relief, The Global Fund to fight AIDS, Tuberculosis and Malaria, UNITAID. Transition to new HIV treatment regimens – procurement and supply chain management issues. Policy brief. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/amds/new_treatment_regimens/en, accessed 30 June 2014).
17. Increasing access to HIV treatment in middle-income countries: key data on prices, regulatory status, tariffs and the intellectual property situation. Geneva: World Health Organization; 2014 (http://www.who.int/phi/publications/hiv_increase_access/en, accessed 30 June 2014).
18. Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach. Geneva: World Health Organization; 2002 (http://data.unaids.org/publications/IRC-pub01/jc354-scalingupguidelinesdoc_en.pdf, accessed 30 June 2014).
19. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. Geneva: World Health Organization; 2003 (revision) (http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf, accessed 30 June 2014).
20. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva: World Health Organization; 2006 (revision) (http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf, accessed 30 June 2014).
21. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. Geneva: World Health Organization; 2010 (revision) (http://www.who.int/hiv/pub/arv/adult2010/en, accessed 30 June 2014).
22. World Health Organization Department of HIV/AIDS, UNAIDS. The treatment 2.0 framework for action: catalysing the next phase of treatment, care and support. Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/arv/treatment/en, accessed 30 June 2014).
23. Short-term priorities for antiretroviral drug optimization. Meeting report (18–19 April 2011, London, UK). Geneva: World Health Organization; 2011 (http://www.who.int/hiv/pub/arv/short_term_priorities/en, accessed 30 June 2014).
24. Update to the optimal list of paediatric ARV formulations. 11–12 September 2013 Meeting Report. Geneva: Interagency Task Team on Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and their Children; 2013 (http://www.emtct-iatt.org/wp-content/uploads/2014/04/IATT-Sept-2013-Updated-Paediatric-ART-Formulary-Report1.pdf, accessed 30 June 2014).
25. Effective medicines regulations: ensuring safety, efficacy and quality. Geneva: World Health Organization; 2003 (http://apps.who.int/medicinedocs/pdf/s4921e/s4921e.pdf, accessed 30 June 2014).
26. Prequalification Programme. A United Nations Programme managed by WHO (http://apps.who.int/prequal/default.htm, accessed 30 June 2014).
27. United States Food and Drug Administration. International programmes (http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm, accessed 30 June 2014).

28. Six years of saving lives through stronger public health supply chains. A report on SCMS contributions to PEPFAR results. United States Agency for International Development; 2011 (http://www.jsi.com/JSIInternet/Inc/Common/_download_pub.cfm?id=12564&lid=3, accessed 30 June 2014).

29. Pharmaceutical manufacturing plan for Africa. Business plan. Geneva: World Health Organization; 2012 (http://apps.who.int/medicinedocs/en/d/Js20186en, accessed 30 June 2014).

30. For detailed data see the Medicines Patent Pool patent status of ARVs (http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs). For pipeline drugs see: The HIV drug pipeline and its patents, August 2013. Initiative For Medicines, Access & Knowledge (I-Mak (http://www.i-mak.org/roadmap, accessed 30 June 2014).

31. World Health Organization, World Intellectual Property Organization, World Trade Organization. Promoting access to medical technologies and innovation. Intersections between public health, intellectual property and trade. Geneva: World Health Organization; 2013 (http://www.who.int/phi/promoting_access_medical_innovation/en, accessed 30 June 2014).

32. Medicines Patent Pool. The Medicines Patent Pool/Gilead licenses: questions and answers (updated August, 2011) (http://www.medicinespatentpool.org/wp-content/uploads/The+Medicines+Patent+Pool+QA+Gilead+Licences+Updated+August+2011.pdf, accessed 30 June 2014).

33. Increasing access to HIV treatment in middle-income countries: key data on prices, regulatory status, tariffs and the intellectual property situation. Geneva: World Health Organization; 2014 (http://www.who.int/phi/publications/WHO_Increasing_access_to_HIV_treatment.pdf, accessed 30 June 2014).

34. MPP and Bristol Myers Squibb sign agreement to further expand access to a key HIV medicine (http://www.medicinespatentpool.org/mpp-and-bristol-myers-squibb-sign-agreement-to-further-expand-access-to-a-key-hiv-medicine, accessed 30 June 2014).

35. Overley J. Mylan ducks $15M Bristol-Myers contract suit over HIV drug (http://www.law360.com/articles/464318, accessed 30 June 2014).

36. Baker BK. Analysis of territorial access issues in the MPP/BMS atazanavir license (http://infojustice.org/wp-content/uploads/2013/12/baker12162013.pdf), accessed 30 June 2014).

37. Licences in the MPP (http://www.medicinespatentpool.org/current-licences, accessed 30 June 2014).

38. MSF Action Campaign. Untangling the web of antiretroviral price reductions: 16th edition, 2013, page 5. Geneva: Medecins sans Frontieres; 2013 (http://www.msfaccess.org/sites/default/files/AIDS_Report_UTW16_ENG_2013.pdf , accessed 30 June 2014).

39. Intellectual property: least developed countries. Responding to least developed countries' special needs in intellectual property. Geneva: World Trade Organization (http://www.wto.org/english/tratop_e/trips_e/ldc_e.htm, accessed 30 June 2014).

40. WTO annual review of the decision on the implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health: report to the General Council. Document IP/C/57, paragraph 19. Geneva: World Trade Organization; 2010 (http://www.wto.int/english/tratop_e/trips_e/ta_docs_e/3_ipc57_e.pdf, accessed 30 June 2014).

41. Fink C, Reichenmiller P. Tightening TRIPS: the intellectual property provisions of recent US free trade agreements. World Bank Trade Note 20. Washington DC: World Bank; 2005.

42. World Health Organization, World Intellectual Property Organization, World Trade Organization. Promoting access to medical technologies and innovation – intersections between public health, intellectual property and trade. Geneva: World Health Organization; 2013 (http://www.who.int/phi/promoting_access_medical_innovation/en/index.html), accessed 30 June 2014).

43. Nakakeeto ON, Elliott BV. Antiretrovirals for low income countries: analysis of the commercial viability of a highly competitive market. Global Health. 2013;9:6. doi: 10.1186/1744-8603-9-6.

44. Grant opposition cases reported on the Initiative For Medicines, Access & Knowledge (I-MAK) website (http://www.i-mak.org/cases, accessed 30 June 2014).

45. Joint WHO/UNAIDS annual consultation with pharmaceutical companies and stakeholders on forecasting global demand of antiretroviral drugs for 2013–2016. Meeting report: 25–26 November 2013. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/amds/amds_arvforecast_meetingreport/en, accessed 30 May 2014).

46. World Health Organization, Futures Institute, UNAIDS. Antiretroviral medicines in low- and middle-income countries: forecasts of global and regional demand for 2013–2016. Technical report. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/111626/1/9789241507004_eng.pdf, accessed 30 May 2014).

47. HIV medicines technology and market landscape. First edition. Geneva: UNITAID; 2014 (http://www.unitaid.eu/images/marketdynamics/publications/HIV-Meds-Landscape-March2014.pdf, accessed 30 June 2014).

48. Harmonized monitoring and evaluation indicators for procurement and supply management systems. Early-warning indicators to prevent stock-outs and overstocking of antiretroviral, antituberculosis and antimalaria medicines. Geneva: World Health Organization; 2011.

49. Coordinated Procurement Planning Initiative. CPP steering committee and technical working group meeting notes, 5 February 2014.

50. The Global Partnership for Development: making rhetoric a reality. MDG Gap Task Force Report 2012. New York: United Nations; 2012 (http://www.who.int/medicines/mdg/mdg8report2012_en.pdf?ua=1, accessed 30 June 2014).

51. Ruxin J, Paluzzi JE, Wilson PA, Tozan Y, Kruk M, Teklehaimanot A. 2005. Emerging consensus in HIV/AIDS, malaria, tuberculosis, and access to essential medicines. Lancet. 365(9459):618–21.

52. Getting products to people: the JSI Framework for Integrated Supply Chain Management in Public Health. Arlington, VA: John Snow, Inc; 2012.

53. The implementation of procurement and supply management M&E indicators in Zimbabwe, 2010–2012. Successes, challenges and trends in PSM performance. A country case study. Geneva: World Health Organization, AIDS Medicines and Diagnostics Service; 2014 (in press).

54. Indicateurs de suivi et d'évaluation des systèmes de gestion des achats et des stocks. Suivi des performances des systèmes de gestion des achats, des stocks et de distribution des ARVs au Mali, 2012. Geneva: World Health Organization, AIDS Medicines and Diagnostics Service; 2014 (in press).

55. Why human resources in supply chain management are important & how can they be strengthened? Copenhagen: People that Deliver/Jon Snow, Inc.; 2014 (in press).

56. United States Agency for International Development (USAID | DELIVER PROJECT, Task Order 1. 2010. Emerging trends in supply chain management: outsourcing, public health logistics in developing countries. Arlington, VA: USAID | DELIVER PROJECT, Task Order 1; 2010.

57. United States Agency for International Development (USAID | DELIVER PROJECT, Task Order 1. 2011. The logistics handbook: a practical guide for the supply chain management of health commodities. Arlington, VA: USAID | DELIVER PROJECT, Task Order 1; 2011.

58. Hausman V, Prashant Y, Daniella B, Herbert B. 30 November 2011. Global Fund: reform needed to regain credibility. Financial Times (http://www.ft.com/cms/s/0/b7392674-1a7c-11e1-ae4e-00144feabdc0.html, accessed 25 June 2014)

59. United States Agency for International Development (USAID | DELIVER PROJECT, Task Order 4. 2012. Supply Chain Management Newsletter. Q4:2012. Arlington, VA: USAID | DELIVER PROJECT, Task Order 4; 2012.

60. Annual progress report year 4: October 2012 to September 2013. Kampala: Securing Ugandan's Rights to Essential Medicines; 2013.

61. Human capacity development assessment for public sector pharmaceutical services in Namibia: strategies to scale up HIV/AIDS programs and ART therapy. Arlington, VA: Management Sciences for Health; 2006 (http://pdf.usaid.gov/pdf_docs/PNADG530.pdf, accessed 25 June 2014)

62. Tjipura-Tjiho D, Mabirizi D, Lazell K, Nwokike J, Saleeb S, Dennis C. A partnership model to improve human resource capacity to deliver pharmaceutical services in Namibia. Presented at the HIV/AIDS Implementers Meeting, June 16–18 2007, Kigali, Rwanda.

63. Managing access to medicines and health technologies. Sterling, VA: Management Sciences for Health; 2012 (http://www.msh.org/sites/msh.org/files/mds3-jan2014.pdf, accessed 25 June 2014)

64. Embrey M, Hoos D, Quick J. How AIDS funding strengthens health systems: progress in pharmaceutical management. J Acquir Immune Defic Syndr. 2009;52 Suppl 1:S34–7. doi: 10.1097/QAI.0b013e3181bbca06.

65. Antiretroviral therapy in the spotlight: a public health analysis in Latin America and the Caribbean. Washington DC: Pan American Health Organization; 2013.

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