# EVIDENCE ON ACCESS TO ESSENTIAL MEDICINES FOR THE TREATMENT OF HIV/AIDS

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# EXECUTIVE SUMMARY

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the developments in access to antiretroviral (ARVs) over the last 10 years in low- and middle-income countries, the factors which have contributed to progress and the lessons which this offers for the future. Specifically, the goal is to:

- Identify the progress that has been made in terms of improved access;
- Review the range of different activities that have contributed to improve access; and
- Evaluate the extent to which improvements in access can be attributed to different interventions, identify potential gaps in our understanding and lessons for the future.

To investigate these issues we have undertaken a literature review with the aim of providing a concise, balanced and up-to-date picture of research on these issues from the perspectives of a wide range of stakeholders.

We selected seven countries to use as case studies to examine in greater detail the policy interventions that may have contributed to improved access to ARVs. We have selected a diverse set of countries that have proved relatively successful at improving access, while representing a range of different circumstances (Botswana, Brazil, India, Mexico, Rwanda, South Africa, and Thailand).[1] Although accepting that seven case studies will always provide only a very partial and selected view of the diverse situation in different countries, these were chosen in order to illustrate the regional environmental differences in Africa, Asia and Latin America, as well as variations in national strategies for combating HIV/AIDS. We have also undertaken interviews with the local industry, academics, NGOs and where possible government officials involved in the HIV programme.

Finally, we have undertaken a statistical analysis testing the relative importance of different factors in determining access or prices. In this analysis we have covered a much wider set of low and middle-income countries, both successful and unsuccessful at improving access to ARVs. We have tested whether the policy interventions identified as potential drivers have actually been important in improving access to ARVs over the last decade.

## ANTIRETROVIRAL THERAPY (ART) REGIMENS AND MEASURES OF ACCESS

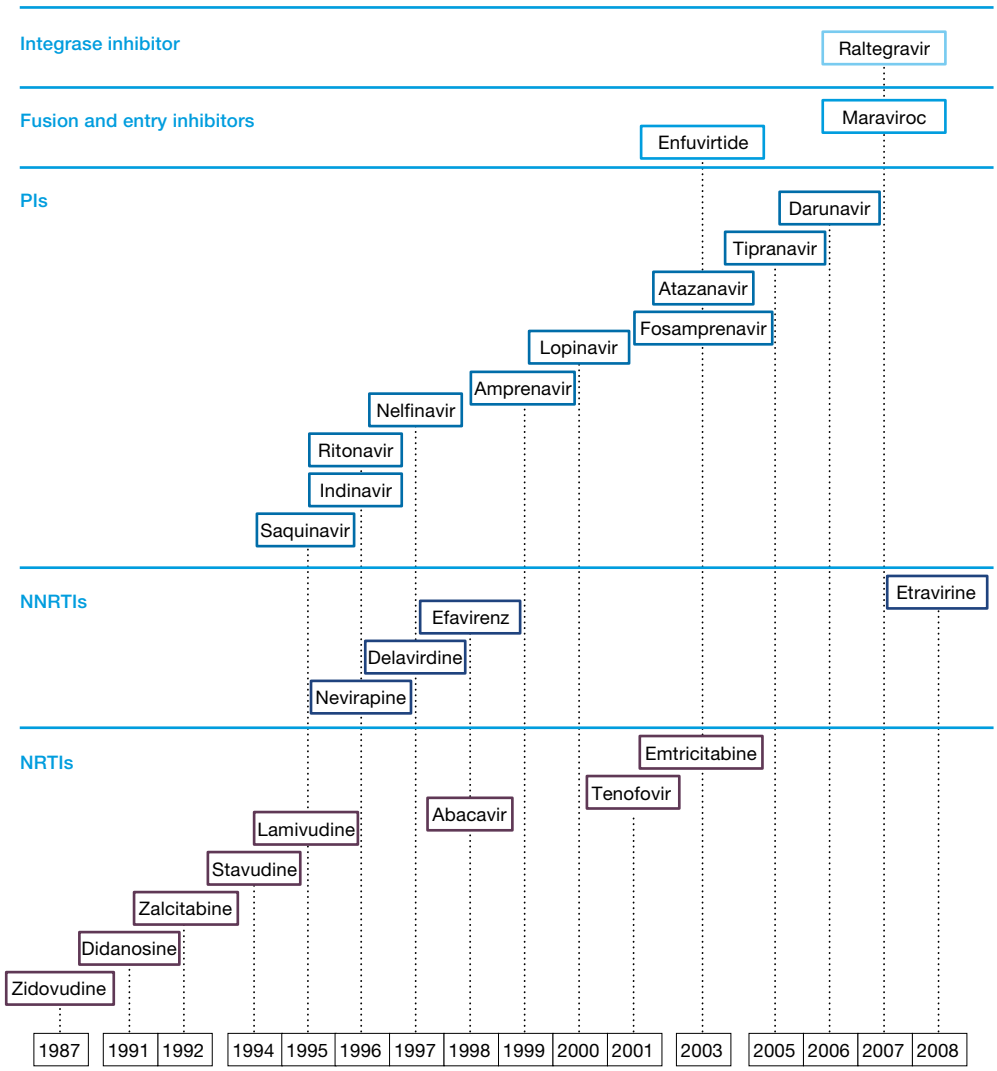
While the first treatments for HIV/AIDS were developed in the late 80s, the most significant developments towards current ART standards were achieved in the mid-90s with the launch of protease inhibitors (PI) and non-nucleoside reverse-transcriptase inhibitors (NNRTI). The new drugs in combined therapy with the older nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI) reduced the development of virus resistance to the medication, which had been one of the main limitations to the long-term efficacy of antiretroviral mono-therapy. The new combined treatment, known as Highly Active Antiretroviral Therapy

1 In classifying countries we adopt the World Bank categorisation which distinguishes between upper middle-income, lower middle-income and low-income. We also distinguish between countries with generalised and concentrated epidemics. In terms of the case studies they can be segmented as follows: upper middle-income with concentrated epidemics — Mexico and Brazil; upper middle-income with generalised epidemics — South Africa and Botswana; lower middle-income with concentrated epidemics — India and Thailand, and low-income and generalised epidemics — Rwanda.

(HAART), typically comprises 2 NRTIs plus 1 NNRTI or alternatively 2 NRTIs plus 1 PI (usually a ritonavir boasted PI). As a number of new ARV drugs have become available, this has diversified the set of treatment strategies that prescribers can use and has offered increased tolerability, reduced side-effects, simplified dosages and expanded the number of alternative treatments available when resistance to first-line treatment is developed.

Figure 1: *Development of new ARV drugs over time by class*

SOURCE: CRA



Given the significant innovation in treatments, the WHO recommended combinations of ARV drugs to be used as first- and second-line treatments have changed three times since the first WHO guidelines in 2002.

The most widely used measure of access is the ART coverage rate — this is the fraction of people eligible for ART that effectively receive treatment. However it has some significant limitations because in practice ART may involve a range of several combinations of ARV drugs and individual HIV/AIDS patients may need specific combinations in order to stabilise their condition. This is further complicated by changes in the clinical criteria for commencing ART treatment based upon diagnostic testing of the CD4 cell count.[2]

## IMPROVEMENT IN ACCESS OVER THE LAST DECADE

In order to reflect on the progress made, it is important to set out the context at the beginning of the decade. As set out in UN Secretary-General Kofi Annan's call for a "war chest" to fight the epidemic, HIV/AIDs was seen as a continent-wide emergency, representing not only the primary cause of death in Africa, but also the biggest challenge to development. Over the last decade, almost every developing country has substantially improved the access of its population to ART, with an estimated 5 million people being treated with ART by 2009. Starting from a situation in which less than 10% of people eligible for ART in low- and middle-income countries had access, this represents significant progress, but still only about 50% of the HIV-infected persons eligible for ART are receiving it across all the middle- and low-income countries.[3]

### Sub-Saharan Africa

By far the largest proportion of people receiving ART in developing countries live in sub-Saharan Africa (SSA). SSA has achieved coverage rates close to 60% in 2009, above the average performance of all low- and middle-income countries. This figure, however, hides wide variation across countries in the area. Eastern and Southern Africa have performed well, while Central and Western African countries have been much less successful at providing access to ART. There has been substantial progress in all of our three case studies in SSA:

- In Botswana the number of patients with HIV/AIDS who receive ART has increased by a factor of four between 2000 and 2005. By 2009, 95% of the population in need of treatment was able to receive it according to the 2006 guidelines (83% according to 2010 WHO guidelines).

- Rwanda has one of the highest rates of ART coverage of any country in Africa, almost 95% in 2009.[4] It is important to recognise that while the coverage rates are quite high, the number of people receiving ART is only 80,000.

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**2** We have based our analysis on measures reflecting the older threshold of 200 cells/mm$^3$. This was raised to 350 cells/mm$^3$ by the WHO in the 2010 HIV/AIDS guidelines. Using the older threshold allows for more consistent data over time. However, it is important to note that access as measured by the new threshold is substantially lower.
**3** The figures are obviously less positive if we were to use instead the new WHO recommended threshold for ART initiation. The change in the threshold, which now recommends ART to be initiated at an earlier stage of disease, increased the number of eligible patients in low- and middle-income countries by 45%, from 10.1 million to 14.6 million. In spite of continued progress, according to the new guidelines only 36% of patients in need of ART's in low- and middle-income countries currently have access to it.
**4** The WHO database provides the same figure of coverage for Rwanda both according to the 2006 and 2010 guidelines.

- South Africa has the largest ART program in the world, but it also has the largest population of people with HIV/AIDS. Access to treatment remains relatively low compared to other middle-income countries, although above the average in SSA: 66% of people needing treatment actually received it in 2009 according to 2006 WHO guidelines (37% according to 2010 WHO guidelines).

**Asia**

Coverage rate has also improved in East and South Asia, although less than in SSA, with coverage rate in 2009 still below 50%. Facing a concentrated epidemic in Asia, with much lower prevalence rates than in SSA, significant progress has been made.

- India has improved access to ARTs over the last decade, but there remains a significant challenge. In 2004, only 28,000 people were receiving ART, out of a population of 622,222 people who needed it (4.5% coverage) as defined by the 2006 WHO guidelines. According to 2006 WHO guidelines, 780,668 people required ART in 2009 and 41% of them received it (26% according to the 2010 WHO guidelines).

- In Thailand the number of HIV/AIDS patients receiving ART has increased steadily over the last decade. In 2002, only 2,000 patients were treated but this has grown to more than 200,000 patients receiving ART in 2009. The level of ART coverage was slightly below 80% using the 2006 WHO guidelines, and slightly above 60% using the new 2010 guidelines.

**Latin America**

Latin America differs from most of SSA or Asia as high coverage rates were already achieved in the late 90s and early 2000s in some countries. Although the number of patients receiving ART has continued to increase during the last decade, coverage rates have been relatively stable. This is clearly demonstrated by:

- Coverage rates in Brazil according to the 2006 WHO guidelines have indeed been stable between 80% and 85% from 2004 to 2009, the period for which the WHO provides records (between 60% and 65% by the 2010 WHO guidelines). High levels of ART coverage had probably been already achieved — at the end of the 90s, since the government committed to guarantee universal access to ART through public financing.

- In Mexico, the number of HIV/AIDS patients receiving ART has increased steadily over the last decade. By 2009, Mexico has been able to offer ART coverage to 71% of HIV/AIDS patients with a cell-count below 200 cells/mm$^3$ and to 54% of patients below 350 cells/mm$^3$.

**Type of ARV, initiation and adherence**

ART coverage rates remain the most commonly used measure to evaluate the achievements in improving access to ART, but need to be complemented by other measures that take into account all of the dimensions of access. For example, the availability of new drugs is an important dimension of access, however, there is relatively limited data on access to newer ARV medicines in low- and middle-income countries. Equally, effective access not only means that patients are initiated on treatment, but that this occurs as early as possible and is maintained over time.

Complementary indicators of access, like the CD4 cell count at initiation of the treatment and the access to newer ARV drugs, show the same evolution over the last decade: significant improvement but falling short of reaching universal access.

**A decade of efforts to improve access to ART**

To understand how this improvement in access has been achieved it is useful to review the range of interventions that have been undertaken. Over the last ten years, the global community of stakeholders with an interest in the challenge presented by the HIV/AIDS pandemics have worked together in an unprecedented fashion.

- Political will — A fundamental change was of course the adoption of universal access to ART as a political priority by the whole international community and most national governments in developing countries. This political commitment, represented by the inclusion of access to HIV/AIDS treatment among the UN Millennium Development Goals, was the prelude of the series of interventions implemented in the subsequent years. The WHO and UNAIDS have had a crucial role leading international action against the HIV/AIDS epidemic. A number of stakeholders have played an important role in building political will locally, particularly civil society, patient groups and NGOs. Political will is often seen as a necessary prerequisite for investing in broadly based HIV/AIDS strategies for prevention, transmission, diagnosis and treatment.

- Domestic health system funding — The management of HIV/AIDS epidemics needs permanent and integrated provision of healthcare services to vulnerable populations and to people living with HIV. Diagnosis, testing, provision of ARV drugs, patient surveillance and support, and programmes to educate and reduce stigma are all components that contribute to guarantee access to ART and ultimately therapeutic success. Structural weaknesses of healthcare systems in developing countries often mean that the provision of all these services is sub-optimal, impeding adequate access to ART by patients. Developing the local infrastructure requires significant allocation of resources. More than half of the $16 billion spent in 2009 came from domestic sources in low- and middle-income countries, mainly public spending.

- International funding — International support for HIV/AIDS has risen dramatically, focusing predominantly on low-income countries, during the last decade, both through bilateral aid and through multilateral organisations. Foreign governments' funding amounted to $7.6 billion in 2009, including both bilateral and multilateral aid. Three quarters of this international funding was provided as bilateral aid, while the rest was distributed through multilateral organisations like the Global Fund and UNITAID. Low-income countries received 78% of all international funds for HIV/AIDS in 2009, while lower middle income countries received 14%. In addition to providing finance for improvement is healthcare infrastructure, prevention and education programmes and acquisition of ART, the multilateral agencies have made a significant contribution through the development of procurement and supply-chain solutions.

- Industry initiatives — Adoption by industry HIV/AIDS drug manufacturers of pricing policies which offer 'not-for-profit' or discounted prices for low-income countries and differentiated low prices for middle income. Currently, most manufacturers of branded ARV drugs operate some mechanism of differential pricing for developing countries. Selective adoption by HIV/AIDS drug manufacturers of voluntary licensing policies to allow middle income country generic manufacturers to compete in certain middle- and low-income countries, often including technology transfer.

- Generic industry — The development of a generic manufacturing base for HIV products is often cited as a significant element of the increase in access. Domestic generic manufacturers have developed in several countries and the Indian generic industry has developed as a major supplier of ARV for certain middle- and low-income countries. They have also invested in development of combination products and manufacturing capacity to meet the rapidly expanding volume demands

- The use of compulsory licensing — In a limited number of cases, national governments have chosen to respond by issuing compulsory licences allowing local generic companies to produce generic versions of patented ARV drugs. In some cases the threat of compulsory licensing may have been used strategically by national governments in negotiations with pharmaceutical companies.

**Understanding the degree to which particular interventions improved access**

Each country examined in this project has responded to HIV/AIDS in a different way, giving stronger emphasis to some forms of intervention than others according to their institutional and economic framework, as well as to the characteristics of their HIV/AIDS epidemic. The third objective of the project is to look at whether some intervention-mixes have proved more effective than others in specific settings by examining the results attained by different countries over the last decade. We have taken two approaches to understanding causality. Firstly we have looked at the history of different case study countries and the degree to which particular interventions have been effective in improving access. Secondly, we have undertaken a statistical analysis testing the relative importance of different factors in determining access or prices.

**Lessons from the case studies**

Although there is wide variation in our case study countries in geography, wealth and the nature of each epidemic, in all of the case studies examined there has been significant progress in expanding access to ART over the last decade. This is summarised in Table 1.

Table 1: *Overview of case studies*

SOURCE: CRA ANALYSIS

| | | Botswana | Brazil | India | Mexico | Rwanda | South Africa | Thailand |
|---|---|---|---|---|---|---|---|---|
| Category | Region | Africa | Latin America | Asia | Latin America | Africa | Africa | Asia |
| | Income group as at 2000* | Upper middle income | Upper middle income | Lower middle income | Upper middle income | Low income | Upper middle income | Lower middle income*** |
| | Type of epidemic | Generalised | Concentrated | Concentrated | Concentrated | Generalised | Generalised | Concentrated |
| Political Will | Year of HIV universal service | 1999 | 1996 | 2004 | 2003 | 2002 | 2004 | 2000 |
| Spending | Share of HIV spending on treatment (including infrastructure, staff, drugs, etc.) | 48.6% on treatment | 83.9% on treatment | 37.2% on treatment | 74.8% on treatment | 40.3% on treatment | Not available | 76% on treatment |
| | Involvement of the international community | 67.3% domestic funded, ACHAP a significant component | 99% domestic funded | 16.5% domestically, Global Fund a significant funder | 99.4% domestic funded | 8.2% public funding, with the rest through Global Fund and bilateral funding | 72.7% public funding, with the rest through bilateral funding | 90% public funding, with the rest through Global Fund |
| IP | Local generic industry | No | Yes | Yes | No | No | Yes | Yes |
| | Government own manufacturer | No | Yes | No | No | No | No (under debate) | Yes |
| | Use of compulsory licensing | No | Yes | No | No | No | No | Yes |
| | Use of Paragraph 6 | No | No | No | No | Once | No | No |
| Access | ART coverage 2004** | 46% | 83% | 5% | 46% | 13% | 5% | 27% |
| | ART coverage 2009** | 95% | 80% | 41% | 71% | 95% | 56% | 76% |

NOTES:
* World Bank categorisation,
** ART coverage according to 2006 WHO guidelines
*** Changed in 2011

Drawing on the experience of the case studies, there are a number of clear themes that emerge regarding the effectiveness of interventions:

- Firstly, the date when the universal ARV programmes were initiated is clearly important and this reflects political will and commitment. It is hardly surprising that programmes starting earlier — in Brazil and Botswana — have been the most successful in achieving high levels of access to ARVs, while the countries with programmes that were not initiated until later have been forced to play catch-up throughout the last decade. In many cases, the countries not initiating their ARV programmes until later initially focused on prevention activities and were more sceptical about the effectiveness of ART. In these countries, coverage rates have risen more slowly and have still not caught up with countries that focused on ART coverage in earlier years.

- Secondly, the speed at which it has been possible to improve access depends on development in the domestic health infrastructure and associated programmes to address stigma. Building up necessary infrastructure takes time and it is one of the primary reasons that countries struggle to raise access levels at an accelerated rate, being instead forced to raise access more gradually over time. There is little doubt that by improving education and reducing stigma, countries can reduce major barriers that exist for patients seeking out voluntary testing and treatment, which is critical for reducing the time to diagnosis and initiating effective treatment regimens.

- Thirdly, the substantial increase in resources from the international community that has been dedicated to promoting health over the last several years has begun to change the trajectory of the HIV/AIDS epidemic in the poorest countries, as evidenced by the case studies of Rwanda, Botswana and South Africa. Only once the Global Fund, PEPFAR, the Gates Foundation and UNAIDS focused resources did access start to improve for the poorest countries. Middle-income countries have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit.

- Fourthly, the innovative industry has contributed to the affordability of ARVs through differential pricing, which emerged as a common practice at the beginning of the decade. This has benefited all of the case studies examined. Each country has its own position regarding their access to differential pricing schemes depending on their income level and the state of their epidemic. Rwanda is a low-income country with a high degree of prevalence, so it has access to the lowest prices. Botswana and South Africa also generally have access to the lowest prices because they are SSA countries with large epidemics. Brazil, Mexico and Thailand are middle-income countries with concentrated epidemics; hence they do not usually have access to the same pricing arrangements as the countries named above. However, they are still usually offered discounted pricing.

- Generic manufacturers have been important in all of the case studies, with the exception of Mexico. However, this varies significantly from country to country. In Brazil, Thailand, India and South Africa domestic suppliers have played an important role for first-line ARTs. In Botswana and Rwanda, Indian generics have played an important role through pooled and direct purchases. This has been clearly the case for first-line treatments and they will play a similar role for second-line treatments in the future. Voluntary licence agreements have played a significant role in the development of generics, particularly in South African and are increasingly important to Indian generics provision of second-line medicines.

- The case studies suggest that the use of compulsory licensing or provision of generics through using Paragraph 6 have not directly played a significant part in improving access. Very few products have been compulsory licensed (and even fewer have used Paragraph 6 provisions).

In conclusion, the key factors explaining access in the case studies varies from country to country. The conclusions from the case studies in terms of whether factors were significant in raising access to the current level are set out in Table 2 below.

Table 2: *Overview of key factors responsible for increasing access in the case studies*

SOURCE: CRA ANALYSIS

| | Rwanda | India | Thailand | Brazil | Botswana | Mexico | South Africa |
|---|---|---|---|---|---|---|---|
| Political will | *** | * | *** | *** | *** | *** | ** |
| Overcoming stigma | ** | * | Unknown | *** | ** | Unknown | ** |
| Domestic healthcare capacity | ** | * | ** | ** | *** | *** | ** |
| International funding | *** | ** | * | * | ** | * | ** |
| Negotiation and procurement | *** | * | * | * | * | ** | *** |
| Generic manufacturers | *** | *** | *** | *** | ** | * | *** |
| Compulsory licensing | * | N/A | * | * | N/A | N/A | N/A |
| Partnerships | *** | ** | ** | * | *** | * | ** |

*** represent a significant factor in raising access to the current level
* represent a minor factor in raising access to the current level

**A statistical analysis of factors affecting access**

As illustrated by the case studies, the approach taken in different markets varies significantly. In any given market, changes in political commitment, funding of medicine purchases, investment in healthcare capacity and negotiation of prices often coincide. In order to try to identify separate impact of different factors and to quantify their relative importance we have undertaken a statistical analysis.

A dataset has been created using ART coverage rates from the WHO, data on expenditure in HIV programmes comes from UNAIDS, country characteristics from the World Bank and data on prices and market structure has been obtained from the WHO Global Price Reporting Mechanism (GPRM). We have undertaken two types of analysis focusing on:

- The factors determining access to ART across countries and over time;
- The factors determining the price of common ARV drugs across countries and over time.

**Access**

This analysis looks at whether there is a correlation between access (as measured by the 2006 WHO definition) and factors capturing country characteristics or proxying for different policy interventions. The estimates from these specifications show that the level of access increases depending on a number of factors. In particular, the level of access is positively correlated with:

- Per capita income in the country;
- The inequality in the distribution of income within the country;
- The prevalence rate;
- The country being outside of the SSA region;
- The time since large-scale ART programmes were started;
- The expenditure on prevention, treatment and management of HIV in total;
- The weight of foreign aid in HIV programmes; and
- The lower cost of ARV treatment.

It is interesting that the importance of the causal factors vary depending on the income of the country. In particular, income per capita and income distribution are only significant for lower middle-income countries. It appears that international funding means that the characteristics of low-income countries are less important in determining access. The cost of ARV drugs is not correlated with ART coverage for upper middle-income countries.

In terms of access, this is consistent with income, spending and the reduction in price of ARVs (particularly for lower income countries) being important factors in the increase in access. We do not find a significant impact for compulsory licensing — this does not mean it did not have an effect, only that other countries were able to achieve the same level of access through other means.

**Prices**

A similar analysis can be undertaken to understand the factors that determine the price of the medicine. In this case we undertook a statistical analysis for a range of first line medicines and for the protease inhibitor most commonly used in second-line treatments (lopinavir+ritonavir). This again used the WHO data on prices of different purchases made by countries in the WHO Global Price Reporting Mechanism. For each product, we looked at whether the price depends on characteristics of the country or the way that it had been purchased. We found that the average price of the ARV drugs is lower:

- The lower is the per capita income in the country;
- When the country is in the SSA region;
- When there are more generics in the market; and
- The more recent is the observation.

The positive correlation between prices and income is consistent with the application of differential pricing. We find this correlation in both branded and generic prices, but as we might expect the correlation appears to be stronger in the former. (This is consistent with branded manufacturers implementing differential pricing schemes but this being less common for generic manufacturers). The positive correlation between prices and income is more significant for newer drugs. In other words, where there is effective generic competition, prices converge on the cost irrespective of the income of the country.

Prices have decreased over time, especially in countries outside SSA. The fact that price reductions are observed even for ARV drugs that were protected during the entire period (efavirenz, lopinavir+ritonavir and tenofovir) suggests that generic competition may not be the only factor triggering price reductions. Increasingly intense class competition among alternative ARV drugs and procurement mechanisms that reinforce buyer power may also have contributed to lower prices. We again do not find a significant effect of compulsory licensing on the level of prices.

**Conclusions and policy implications**

There has been substantial progress in providing access to HIV patients over the last ten years. ART coverage in low- and middle-income countries has increased from 12% in 2003 to 54% in 2009, measured according to the 2006 WHO guidelines. This is due to many different factors working together in often complex ways. Many challenges clearly remain: there is a large under-served population and there are types of patient that are still particularly badly served, paediatrics for example.

A major source of uncertainty which hangs over all future policy formulation is the speed at which mutations will create resistant strains of HIV. As the virus evolves, the products that have made significant progress possible in the last decade will become less effective and new medicines will be needed. Ensuring that the lessons learnt through the last decade feed into the future plan is therefore vital:

- Political commitment to HIV/AIDs, encouraged by civil society and NGOs, has played a significant role in changing attitudes, committing domestic resources and encouraging the industry to increase its contribution.
- International funding has been a key part of increased access for the lowest income countries. This needs to be maintained if further progress is to be achieved, particularly in the poorest countries.

- A holistic programme is needed to allow the different components to reinforce each other. As observed increasing access to treatment reduces stigma, that itself is a barrier to patient's seeking treatment. Recent research shows that ART also reduces transmission rates. Prevention and treatment are complements not substitutes. As shown in recent research, high levels of access can improve prevention.

- The generic industry and the innovator industry contribute in different ways to addressing the epidemic. Generic companies are able to supply low-income countries more efficiently and more cheaply than innovating companies. Innovators have been responsible for all of the significant new medicines treating HIV over the last decade. There appears wide agreement that generics should play a substantial role in the provision of second-line medicines for the lowest income countries (in fact they already are), but the impact of competition on prices will only emerge as scale is achieved. Indian generics will play a crucial role for second line products as they did for first line products.

- Innovating companies should compete to develop new medicines (working collaboratively where appropriate) and they should also compete in terms of making sure there is access to their medicines. This has prompted innovation in different mechanisms for providing access and substantial benefits. This has also resulted in added complexity. Raising awareness of how prices are structured across countries can add value. The industry should work with partners to get the best balance between innovative programmes to encourage access and ensuring purchasers are aware of and understand different schemes.

- For middle-income countries, there is an existing intellectual property (IP) regime and prices of medicines will be higher than the lowest income countries as generics are not able to compete in the market. Preferential pricing means that this will be based on ability to pay — negotiation has been effective at lowering prices over time — and ultimately generics will enter as patent protection ends. This is appropriate if it is agreed that middle-income countries should pay some element of the cost of innovation. Without (IP), prices will be lower today but incentives to innovate will be correspondingly lower in the future when further innovation will be needed.

# 1

# INTRODUCTION

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the developments in access to antiretroviral (ARVs) over the last 10 years, the policy initiatives and other factors which have contributed to progress and the lessons which this offers for the future. Specifically, the goal is to:

- Identify the progress that has been made in terms of improved access;
- Review the range of different activities that have contributed to improved access over the last decade, ranging from building healthcare capabilities, multilateral funding mechanisms, such as the contributions of the Global Fund and PEPFAR, and industry initiatives such as voluntary licensing and differential pricing; and
- Evaluate the extent to which improvements in access can be attributed to different mechanisms, identify potential gaps in our understanding and lessons for the future.

## 1.1 BACKGROUND TO THE PROJECT

When a new viral pathogen, HIV, was identified as the likely cause of AIDS in the early 1980s, there were only a few antiviral drugs that were available. Over the next two decades, the HIV/AIDS epidemic was slowly recognised as a global health priority with the biggest challenge facing developing countries, especially in sub-Saharan Africa (SSA), with limited capacity to control the infection. At the same time, significant progress was being made developing today's therapies for the treatment of AIDS, based on a number of antiretroviral drugs with different mechanisms of actions.[5] Prevention efforts since the early stages of the epidemic in the 80s and treatment programmes since the 90s proved effective at controlling the epidemic. However, access to effective treatment strategies in resource-constrained settings was seen as a significant issue that needed to be addressed. The starting point for this report is the fourth World Trade Organization (WTO) Ministerial meeting held in Doha, Qatar in November 2001. This resulted in a declaration stressing the importance of interpreting the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement in a way that supports public health, by promoting both access to existing medicines and the creation of new ones. This was adopted in November 2001: "Declaration on the TRIPS agreement and public health".[6] It recognised the seriousness of the public health problems afflicting many middle-income and low-income countries[7], especially those resulting from HIV/AIDS and other epidemics. This set out how the development of access to pharmaceutical medicines could be undertaken within the context of the improvement in intellectual property (IP) protection agreed under TRIPS. In other words, the need to take into account the importance of IP protection while recognising the concern about prices. In particular, the declaration sets out:

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**5** De Clerq (2007), "The design of drugs for HIV and HCV",Nature Reviews Drug Discovery, 6: 1001-18.
**6** Available from http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm
**7** In the report we use the standard World Bank definitions of low-, middle- and high-income countries. Low-income and middle-income economies are sometimes referred to as developing economies. http://data.worldbank.org/about/country-classifications

- Provisions for the use of compulsory licences in Paragraph 5;

- Recognition that countries with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement and other expeditious solutions might need to address these problems in Paragraph 6;

- The commitment of developed country members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least developed country members in Paragraph 7; and

- Least developed country members are not obliged, with respect to pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, also in Paragraph 7.[8]

This project aims to review the contribution that these provisions have had in the development of access to antiretroviral therapy (ART) within the wider context of other major initiatives to inject international funding, in order to drastically upgrade the necessary infrastructures for diagnosis, treatment and effective follow-up interventions for patient populations scattered throughout these countries.

The role of patents in medicines in developing countries remains highly controversial.[9] Some stakeholders are concerned that enforcing patent rights is based on commercial and market-based considerations, thereby preventing access to, or leading to an increase in the prices of, essential medicines such as HIV/AIDS drugs.

There continues to be concern regarding the price of new ARVs restricting access to patients and that patents are blocking the affordable production of these drugs. There are concerns that the flexibilities (for example, Paragraph 6) do not work effectively and new, innovative mechanisms should be supported to increase access to drugs in all developing countries, such as the Medicines Patent Pool.[10]

## 1.2 METHODOLOGY

The methodology for the project has a number of different elements:

- A literature review: Our aim is to provide a concise, balanced and up-to-date review of the current literature, recognising that over many years the debate on access to medicines has attracted interest and commentaries from a wide range of stakeholders, including academic, clinical and economic experts, WHO, World Bank, many contributing charities, NGOs, national governments and the innovative and generic sectors of the pharmaceutical industry. In this light, we briefly discuss the evolution of the epidemic and the changes in access to ARVs and used this to choose the case studies.

- Case studies: We selected seven countries to examine in greater detail (Botswana, Brazil, India, Mexico, Rwanda, South Africa and Thailand). Although accepting that seven case studies

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**8** It is important to distinguish between least developed countries and low-income countries as defined by the United Nations and World Bank respectively. Least developed countries are defined by income and the human development index.
**9** "HIV AND AIDS IN AFRICA: COMPULSORY LICENSING UNDER TRIPS AND DOHA DECLARATION" 9/30/2010 LL.M. Columbia University Law School Ufuoma Barbara Akpotaire
**10** "MSF Statement at UN High-Level Meeting on HIV/AIDS" available at http://www.msfaccess.org/main/hiv-aids/stop-the-virus-no-excuse-for-neglecting-10-million-people-with-hiv/msf-statement-at-un-high-level-meeting-on-hivaids/

can only provide a very partial and selected view of the diverse situation in different countries, these were chosen in order to understand:

– Implications from the timing of the initiation of the ART programme. In particular, what lessons might be learned from countries that had started their response early, as in Brazil and Botswana, compared to those that were relatively late in establishing national plans such as — South Africa.
– Different patterns in the nature of the epidemics and the response to HIV/AIDS in Africa, Asia and Latin America, with particular attention to those countries where the HIV epidemic has been of most concern for the period under consideration (including South Africa, Botswana, Rwanda and Thailand).
– Variations in national strategies for combating HIV/AIDS; notably the setting of a balance between investment in treatments versus prevention and the use of different approaches. For example, in Mexico or India.
– Methods to use generic manufacturers. For example, we give particular attention to Brazil and Thailand, which have sought to use compulsory licencing and the development of generic manufacturing in India.

- Interviews: In each of the case studies we have reviewed the local literature on the lessons over the last ten years. Where possible we have undertaken interviews with the local industry, academics, NGOs and government officials involved in the HIV programme.[11]

## 1.3 STRUCTURE OF THE REPORT

The rest of the report is structured as follows:

- In Chapter 2, we look at the nature of the HIV epidemic since 2000 and how access to ARVs has changed;

- In Chapter 3, we examine the range of policies that have been developed in response to the epidemic and the role of different stakeholders drawing on wider international experience;

- In Chapter 4, we look at the lessons we can draw from the seven case studies;

- In Chapter 5, we set out a statistical analysis of the factors that contribute to the increase in access.

11 We have undertaken 20 interviews including local trade associations and manufacturers, the Global Fund, Oxfam, Red Cross, procurement department and government departments.

# 2

# TRENDS IN THE HIV/AIDS EPIDEMIC AND ACCESS TO ART OVER THE LAST DECADE IN DEVELOPING COUNTRIES

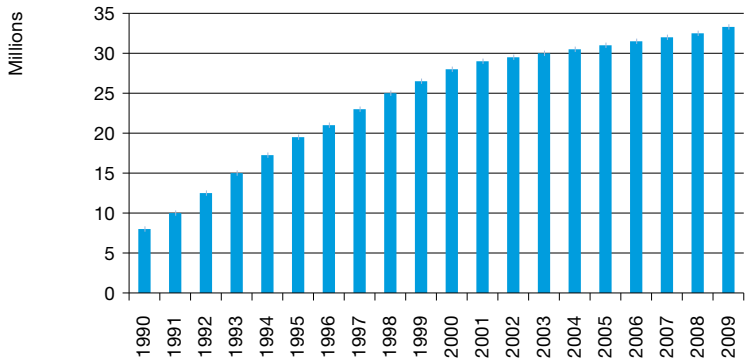
In this chapter, we first review the evolution of the epidemic and how this varies across countries and regions (largely drawing from UNAIDS statistics) as context for the analysis to follow; we then look at measures of access to ARV and how it has changed over the last ten years.

## 2.1 MAIN TRENDS OBSERVED IN THE EVOLUTION OF EPIDEMIOLOGIC INDICATORS

According to UNAIDS estimates, the number of people living with HIV/AIDS in the world has increased over the last decade, from 26.2 million in 1999 to 33.3 million in 2009.[12] This represents a 27% increase, significantly lower than the 70% increase that occurred between 1990 and 1999, which is reflected in Figure 2. Although in this report we are interested in the changes observed during the last decade, it is useful to compare the experience of the last ten years with that of the 90s. For instance, while the absolute number of people living with HIV has increased during the last 10 years, it has done so at a significant lower rate than during the previous decade. Hence, in this section we present epidemiologic data for the period 1990-2010.

Figure 2: *Number of people living with HIV/AIDS worldwide*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

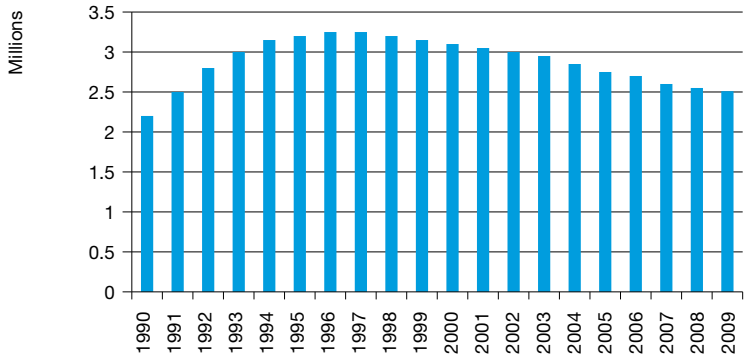



The number of new HIV infections worldwide has continuously fallen since the mid-90s. As shown in Figure 3, the number of new HIV infections was estimated at 2.6 million in 2009, fewer than the 3.2 million infections estimated in 1997, the year in which the maximum number of new infections was observed.[13] However, while this decline has been significant, it has not been enough to decrease the total number of people living with HIV/AIDS.

**12** UNAIDS database (extracted from http://www.aidsinfoonline.org/)
**13** UNAIDS database (extracted from http://www.aidsinfoonline.org/)

Figure 3: *Number of new HIV infections worldwide*

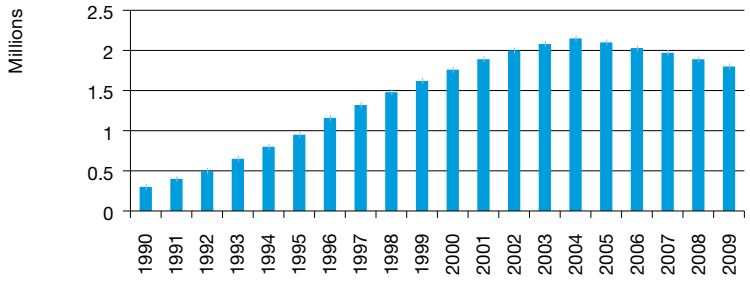
SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




Mortality levels have also decreased during the second half of the last decade. The number of AIDS-related deaths worldwide peaked at 2.1 million in 2004, but it has since fallen to an estimated 1.8 million deaths in 2009.[14]

Figure 4: *Number of AIDS-related deaths worldwide*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

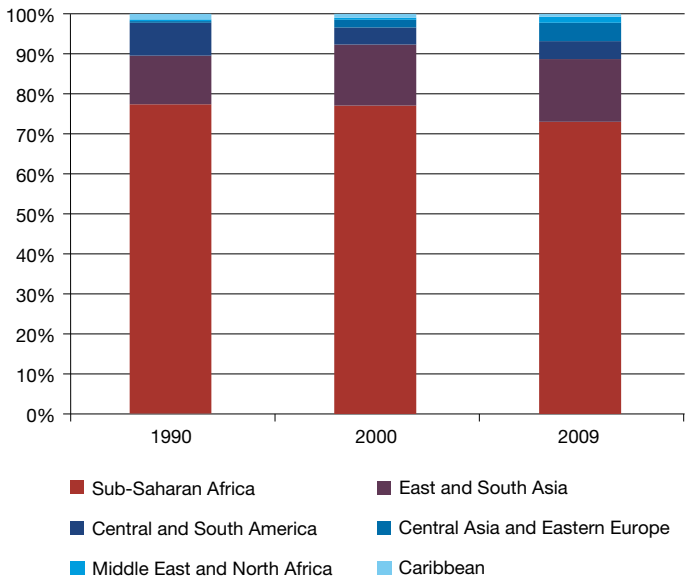



These general patterns hide substantial variation across regions, both in terms of the population groups affected by the epidemic and the evolution of the main epidemiological indicators across time. The largest proportion of HIV-infected people live in SSA and this has been true for the last two decades, as shown in Figure 5.

**14** UNAIDS database (extracted from http://www.aidsinfoonline.org/)

Figure 5: *Shares of people living with HIV/AIDS by region*

SOURCE: CRA USING UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




## 2.1.1 Generalised epidemic in sub-Saharan Africa

According to UNAIDS, in 2009, 22.5 million people were living with HIV/AIDS in the SSA region, which represents more than 70% of the global total.[15] The large share that SSA represents of the global HIV burden explains why the evolution of that region's epidemiological indicators closely resembles that of global indicators. In sub-Saharan Africa, the number of new HIV infections has declined since the mid-90s and the number of AIDS-related deaths has decreased during the second half of the past decade, leading to a slower growth in the number of people living with HIV in the region. This is shown in Figure 6 to Figure 8.

A defining characteristic of the HIV/AIDS epidemic in SSA is its nature of generalised epidemic[16] affecting all population groups. In addition to that, HIV prevalence in the countries of the region is substantially higher than in any other region. This is particularly true for Southern Africa, with levels of HIV prevalence[17] between 10% and 25% in 2009.[18]

**15** UNAIDS database (extracted from http://www.aidsinfoonline.org/)
**16** Generalised epidemic: high level — where HIV is firmly established in the general population and sexual networking is sufficient to sustain an epidemic independent of sub-populations at higher risk of infection. Concentrated epidemic: low level — where HIV is concentrated in groups with behaviours that expose them to a high risk of HIV infection. (UNAIDS Global Report Methodology 2010)
**17** The AIDS / HIV prevalence rate refers to the percentage of people tested who were found to be infected with HIV in a given population. The incidence rate is the number of new cases per population.
**18** UNAIDS database (extracted from http://www.aidsinfoonline.org/)

Figure 6: *Number of people living with HIV/AIDS in sub-Saharan Africa*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

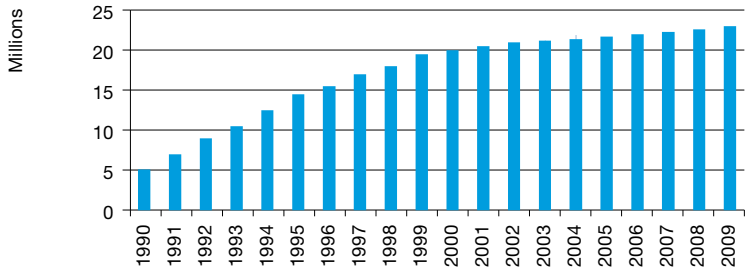



Figure 7: *Number of new HIV infections in sub-Saharan Africa*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

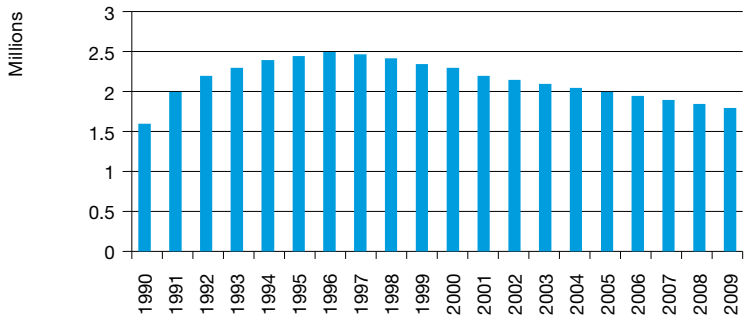
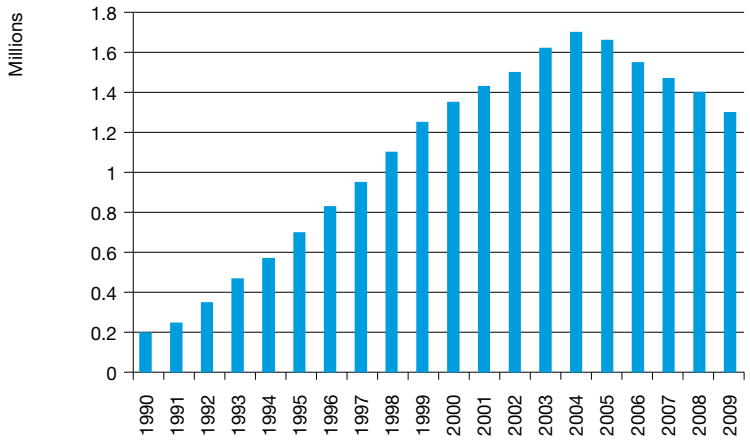



Figure 8: *Number of AIDS-related deaths in sub-Saharan Africa*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)



While its generalised character is the most defining factor of the HIV/AIDS epidemic in sub-Saharan Africa, there is increasing evidence that certain risk factors affecting specific population groups are also relevant.[19]

By looking at the case-study countries, we can illustrate how different countries in the region have experienced distinct evolutions of the HIV/AIDS epidemic. Each of those countries share the generalised character of the epidemic, but there remain substantial differences between them.

In Botswana, HIV/AIDS has had an enormous impact on the entire population. Botswana had a rapid growth in HIV/AIDS prevalence throughout the 1990s before finally peaking in the early 2000s. This growth was consistent with the spread of the epidemic in other countries in sub-Saharan Africa. In more recent years, the spread has markedly slowed, causing the total number of people living with HIV/AIDS to grow at a much slower pace while the prevalence rate has fallen slightly.

The slower growth of the affected population and the subsequent decline in prevalence rates is directly related to the steep decline in the number of new HIV infections since the peak that occurred in 1996 and 1997. While the 2% incidence rate in 2009 still represents a significant number of new HIV infections, it is a large decrease from the nearly 6% incidence rates that occurred a little over a decade earlier. The number of deaths from HIV peaked in 2003 but since then, it has been consistently declining, which reflects the increased availability and use of ARVs in Botswana.

While the number of deaths and the incidence rate have both declined significantly in recent years, the continuing growth of the overall prevalence of HIV/AIDS in Botswana reflects the seriousness of this epidemic.

Rwanda also faces a generalised epidemic, but with significantly lower levels of prevalence than Botswana. According to data from UNAIDS, prevalence rates have declined steadily since 1990, from a high of just over 5% to below 3% in 2009. The evolution of the absolute number of people living with HIV in Rwanda is more difficult to interpret due to the effects of the genocide that occurred in 1994 and the internal strife in the years immediately before and after that. The total number of people living with HIV/AIDS has increased moderately from 160,000 in 1990 to 170,000 in 2009, but there have been fluctuations during that time period. Incidence has also fluctuated since 1990, but in absolute terms, it has declined from 21,000 new infections in 1990 to 8,800 in 2009. From 2001 to 2006, the incidence rate fell rapidly, after which it levelled off at just over 0.1% before rising slightly to just under 0.2% in 2009.

After 1990, the number of deaths related to HIV/AIDS first increased, from 8,400 in 1990 to a peak of 15,000 people annually from 2000 to 2004. It wasn't until 2005 that the number of deaths began to decline, but there has been a steep drop since then and there were an estimated 4,100 deaths in 2009.

In contrast, South Africa continues to face one of the most challenging HIV/AIDS epidemics in the region. The number of people living with HIV in South Africa increased rapidly through the 90s, with growth not slowing until the last ten years. The prevalence rate rose from under 1% in 1990 to a peak of 18% in 2004 where it has remained since. Incidence peaked in 1998 when more than 700,000

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**19** "UNAIDS REPORT ON THE GLOBAL AIDS EPIDEMIC 2010"
available at http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf

new cases of HIV were recorded. Since then, incidence has fallen at a declining rate, and in 2009, there were still close to 400,000 new cases of HIV. The incidence rate has fallen off its peak of 3.2% in 1997 to 1.5% in 2009. The number of deaths from HIV continued to increase until 2005, and then held steady for several more years. It wasn't until 2008 that the number of deaths began to decline, several years after declines began in Botswana and Rwanda.

### 2.1.2 Concentrated epidemic in American and Asian developing countries

Asia and Latin America present substantially different scenarios, where the HIV/AIDS epidemic is concentrated in certain population groups exposed to risk factors that facilitate the transmission of HIV. Rates of prevalence for the general population in these regions are much lower than in sub-Saharan Africa, with Thailand the only country where prevalence is close to 1%.

The number of people living with HIV at the beginning of the 90s was slightly larger in Asia than in Latin America, but in twenty years the difference has increased considerably. Latin American countries were better able to contain the number of new HIV infections and the growth of the epidemic was slower. The number of people living with HIV grew from 550,000 in 1990 to 1.4 million people in 2009. In Asia, the number of new HIV infections has been much higher over the whole period and only started to decrease during the last decade. As a result, prevalence has grown significantly and an estimated 4.9 million people were living with HIV in 2009 in Asia, more than five times the estimated figure in 1990. AIDS-related deaths in Latin America remained below 60,000 per year for the whole period, and have stayed relatively constant since 2005. To a great extent this was due to early adoption of antiretroviral therapy, especially in Brazil (as discussed in the next chapters) which has the highest number of HIV infections in the region. In contrast, the number of AIDS-related deaths in Asia increased steeply until the second half of the last decade, with a peak of more than 300,000 deaths in 2007. Figure 9 to Figure 14 shows the evolution of prevalence, incidence and AIDS-related deaths in Asia and Latin America.

Figure 9: *Number of people living with HIV/AIDS in Asia*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

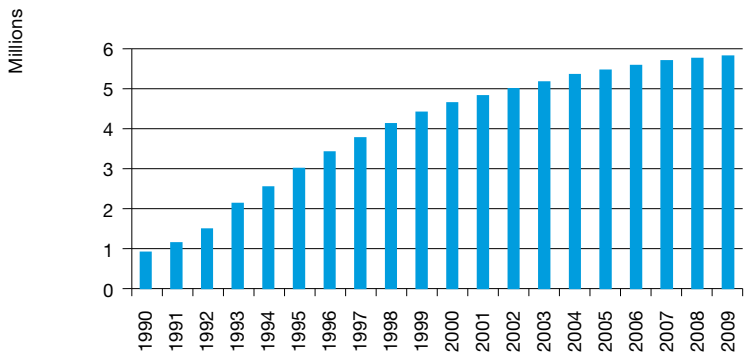


Figure 10: *Number of new HIV infections in Asia*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

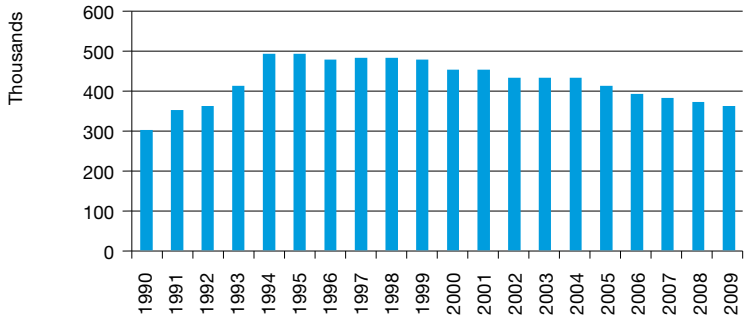



Figure 11: *Number of AIDS-related deaths in Asia*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

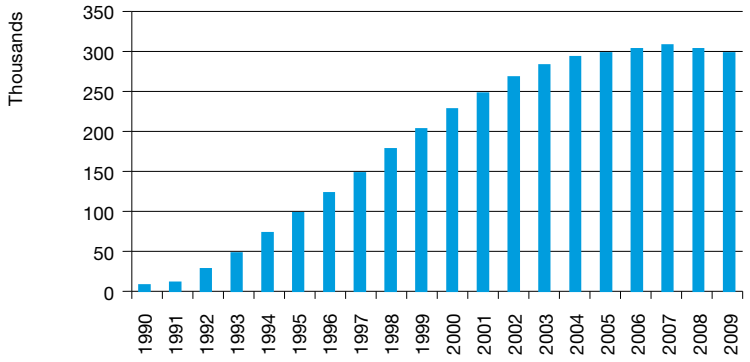



Figure 12: *Number of people living with HIV/AIDS in Central and South America*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

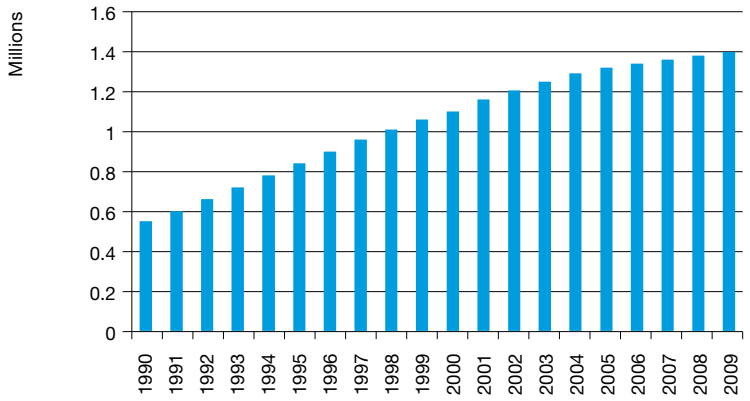


Figure 13: *Number of new HIV infections in Central and South America*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

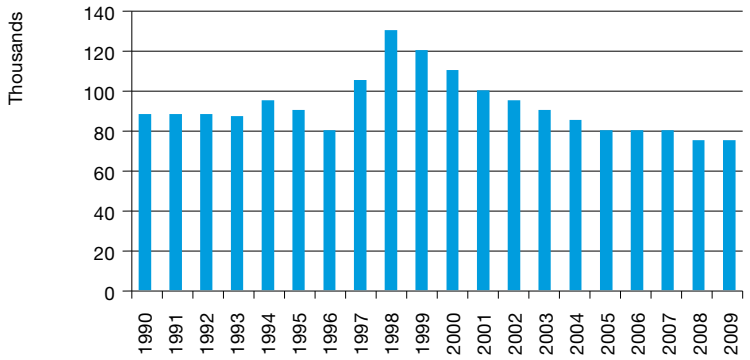
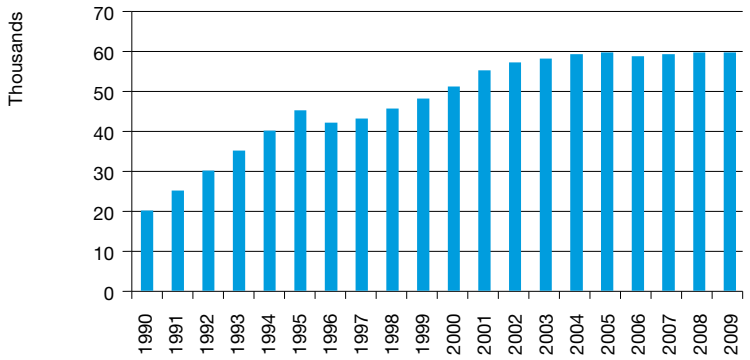



Figure 14: *Number of AIDS-related deaths in Central and South America*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




These figures hide substantial variation between countries within each region. In Asia, incidence rates fell in India, Nepal and Thailand between 2000 and 2009, remained stable in Malaysia and Sri Lanka, but increased significantly in Bangladesh and the Philippines.[20] The concentrated pattern of the HIV/AIDS epidemic in Latin America also shows variations across countries.[21] Even within the countries, the geographic distribution of the epidemic is uneven and there are larger proportions of HIV-infected people in particular regions of each country. This is especially true in large countries like India.[22]

**20** Based on UNAIDS data (extracted from http://www.aidsinfoonline.org/)
**21** However, it can be said that most of the HIV epidemics in the region are concentrated in men who have sex with men, for whom relatively high levels of HIV prevalence have been estimated. Injecting drug users are another population group in which the HIV epidemic is concentrated, as well as sex workers to a lesser extent. HIV transmission through heterosexual sexual intercourse has increased but remains low. UNAIDS Global Report 2010
**22** The same can be said with respect to the transmission modes. In general it can be said that the epidemic in Asia remains concentrated among injecting drug users, sex workers and their clients, and men who have sex with men. The relative importance of each of these factors, however, varies across countries. UNAIDS Global Report 2010

Our case-study countries from Asia and Latin America provide an illustration of the concentrated epidemics that characterise these regions. Brazil has registered relatively low and stable levels of HIV/AIDS prevalence among the general population over the last two decades, at 0.4%.[23] While the number of new infections in Brazil was relatively high at the beginning of the 90s, it was rapidly reduced during the mid-90s. The incidence rate reached its minimum between 1994 and 1997, most likely as a consequence of the emphasis given to prevention efforts in Brazil during the early stages of the epidemic. Since 1996, deaths have first decreased and then stabilised, despite the increasing number of people living with HIV/AIDS. Relative to the total population, the death rate has declined over the last ten years.

The levels of prevalence are higher within vulnerable populations, which include sex workers, men who have sex with men and injectable drug users. While there is evidence that these vulnerable populations accumulate the highest proportion of HIV/AIDS cases, there remains a lack of data on actual prevalence and incidence rates in these populations.[24] The HIV/AIDS epidemic in Brazil also has considerable regional differences. Since the first cases were diagnosed in the early 80s, the epidemic in Brazil has been found primarily in urban settings and concentrated in the south and south-east regions, notably the Rio de Janeiro–Sao Paulo corridor. This pattern is still observed, though the epidemic has gradually expanded toward rural regions in the north and north-east of the country as well.

Mexico has registered relatively low and stable levels of HIV/AIDS prevalence among the general population over the last two decades and it has a prevalence rate of 0.3%. While the number of HIV/AIDS patients has increased during this period, the growth rate has been similar to the growth rate of the adult population, leaving the prevalence rate unchanged. Although the number of new infections has been increasing over the last two decades, from 15,000 new infections in 1990 to around 20,000 in 2007, the level of incidence has remained constant at 0.04%. Examining the number of deaths related to AIDS over time, the introduction of new ARV drugs in 1996 constitutes an inflexion point. Between 1990 and 1996, the number of deaths per one hundred thousand inhabitants in Mexico increased from 1.8 to 4.6. Since then, this figure has remained stable at around 4.3 deaths per one hundred-thousand inhabitants.

A number of studies have attempted to estimate the levels of HIV/AIDS prevalence in vulnerable populations, and they have revealed a concentrated pattern.[25] The HIV/AIDS epidemic in Mexico presents a unique situation as a result of the intense migration flows across the country towards the US. Higher levels of prevalence are observed in border regions in the north of the country and in rural areas crossed by migration routes.[26]

India has one of the largest HIV-positive populations in the world, in spite of its relatively low levels of prevalence. In 1990, there were an estimated 250,000 people infected by HIV; at its peak in 2002, HIV had infected 2.6 million people. Since then, the infected population has fallen slightly to 2.4 million people in 2009. Prevalence rates reached the maximum of 0.4% from 1998 to 2007.

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**23** UNAIDS data (extracted from http://www.aidsinfoonline.org/)
**24** Fonseca and Bastos (2007), "Twenty-five years of the AIDS epidemic in Brazil: principal epidemiological findings, 1980-2005", Cad Saude Publica, 23(3): 333-344.
**25** Magis Rodriguez and Hernandez Avila (2009), "Epidemiologia del SIDA en Mexico", in "25 años de SIDA en Mexico: logros, desaciertos y retos".
**26** Magis Rodriguez and Hernandez Avila (2009)

Incidence grew significantly during the 90s, reaching 3.4% in 1997, but it steadily declined during the last decade, being at 1.2% in 2009. The number of deaths from HIV increased drastically as the epidemic spread, from 5,300 in 1990 to 200,000 in 2005. Since then, the number of deaths has declined slightly; 170,000 deaths from HIV in 2009, down from 190,000 in 2008.

Six states with high prevalence of HIV account for two-thirds of the HIV burden in India. Trends in prevalence vary between the many districts of India, with some of the districts reporting increasing prevalence while some report decreasing prevalence since 2007. Most evidence shows that while there has been a decline in the overall prevalence of HIV in India, this has been a result of a decline in the high prevalence states, while prevalence has increased in states that historically had low prevalence.

Thailand has registered relatively high levels of HIV/AIDS prevalence in comparison to other countries in the region. HIV prevalence in Thailand reached the 2% in the mid-90s and has been falling since then, currently registering levels of prevalence slightly above 1%. In spite of this decrease in prevalence, Thailand continues to be the country with the highest level of prevalence in the region. The decrease in prevalence rates has been a consequence of the sharp reduction in the number of new HIV infections during the 90s. The incidence rate was above 0.5% in the early 90s, with around 150,000 new HIV cases every year. By 2000, the number of new cases was already below 30,000 and has continued to fall during the last decade. Around 10,000 new HIV cases are currently registered yearly in Thailand, which represents and incidence rate of 0.03%. The number of HIV-related deaths grew steadily during the 90s and reached an inflexion point in 2000, when 56,000 people died from HIV/AIDS. The death rate fell sharply until 2005 and since then it has shown a moderate growth. 28,000 HIV/AIDS patients died in 2009, half the figure ten years before.

### 2.1.3 Specific trends in other world regions

Other regions of the developing world represent a much lower share of the total number of people living with HIV, with the exception of Eastern Europe and Central Asia, where the HIV epidemic has grown to considerable magnitude. In Eastern Europe and Central Asia, the number of people living with HIV/AIDS increased significantly during the first half of the last decade. Although the number of new HIV infections has stabilised since then, high rates of HIV transmission continue to occur in the networks of people who inject drugs and their sexual partners.[27]

The HIV epidemic is also stabilised in the Caribbean, where the number of people living with HIV and the number of new infections have both remained constant with little variability for the last decade.

In contrast, the HIV epidemic has been growing in the Middle East and North Africa during the last ten years, although HIV prevalence and incidence in the region remain among the lowest in the world.

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**27** "UNAIDS REPORT ON THE GLOBAL AIDS EPIDEMIC 2010"
available at http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf

## 2.2 ANTIRETROVIRAL THERAPY FOR THE TREATMENT OF HIV/AIDS

In this section we describe the current WHO recommended treatments, discuss the measurement of access to ART and review evidence on the improvement in access over the last decade in developing countries.

### 2.2.1 Antiretroviral therapy

The current treatment paradigm for HIV/AIDS was developed in the mid-90s when a new generation of antiretroviral drugs became available. The first significant developments in ART were the protease inhibitors (PI) and non-nucleoside reverse-transcriptase inhibitors (NNRTI). The new drugs in combined therapy with the older nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI) reduced the development of virus resistance to the medication, which had been one of the main limitations to the long-term efficacy of antiretroviral mono-therapy. The new combined treatment is known as Highly Active Antiretroviral Therapy (HAART). Current first-line HAART typically comprises 2 NRTIs plus 1 NNRTI or alternatively 2 NRTIs plus 1 PI (usually a ritonavir boasted PI).

WHO's recommended combinations of ARV drugs for first- and second-line treatments have changed several times during the last decade. Since the first WHO guidelines for HIV/AIDS treatment were published in 2002, they have been revised three times. Changes in WHO guidelines are generally incorporated by individual countries shortly after they are released. Regular updates of treatment guidelines are an expected consequence of the significant advances that research in the field over the last several years.

As new ARV drugs have become available, the set of treatment strategies that prescribers can use has expanded. New ARV drugs have increased tolerability, reduced side-effects, simplified dosages and expanded the number of alternative treatments that are used when resistance to first-line treatment is developed. Successive versions of WHO guidelines have progressively incorporated new lessons that have been learned from experiences with older drugs and the results of recent scientific research. Figure 15 shows recommended first-line ARV combinations in the four different guidelines published by WHO during the past decade.

Table 3: *ARV drugs that have obtained FDA[28] market authorisation*

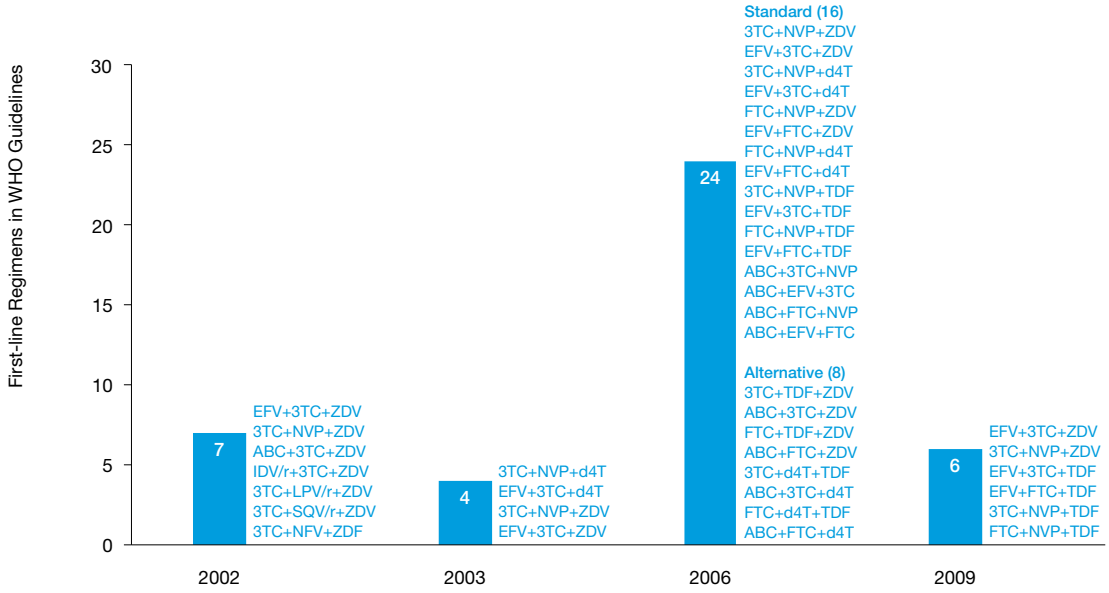
SOURCE: HTTP://DEPTS.WASHINGTON.EDU/HIVAIDS/ARVRX/CASE2/FIG3D.HTML

| Antiretroviral class | Active principle | Year of FDA approval |
|---|---|---|
| Nucleoside and nucleotide reverse-transcriptase inhibitors (NRTI) | Zidovudine (AZT) | 1987 |
| | Didanosine (ddI) | 1991 |
| | Zalcitabine (ddC) | 1992 |
| | Stavudine (d4T) | 1994 |
| | Lamivudine (3TC) | 1995 |
| | Abacavir (ABC) | 1998 |
| | Tenofovir (TDF) | 2001 |
| | Emtricitabine (FTC) | 2003 |
| Non-nucleoside reverse-transcriptase inhibitors (NNRTI) | Nevirapine (NVP) | 1996 |
| | Delavirdine | 1997 |
| | Efavirenz (EFV) | 1998 |
| | Etravirine (ETR) | 2008 |
| Protease inhibitors (PI) | Saquinavir (SQV) | 1995 |
| | Indinavir (IDV) | 1996 |
| | Ritonavir (RTV) | 1996 |
| | Nelfinavir (NFV) | 1997 |
| | Amprenavir | 1999 |
| | Lopinavir (LPV) | 2000 |
| | Atazanavir (ATV) | 2003 |
| | Fosamprenavir (FPV) | 2003 |
| | Tipranavir (TPV) | 2005 |
| | Darunavir (DRV) | 2006 |
| Fusion and entry inhibitors | Enfuvirtide (T20) | 2003 |
| | Maraviroc (MVC) | 2007 |
| Integrase inhibitor (II) | Raltegravir (RAL) | 2007 |

**28** The US Food and Drug Administration (FDA).

Figure 15: *Recommended first-line ART in WHO guidelines*

SOURCE: WANING ET AL. (2010)[29]




- The first WHO HIV/AIDS guidelines were released in 2002. They recommended seven regimens, all of which were based on the use of zidovudine, the first NRTI that became available in the late 80s, and lamivudine. Different types of combinations were recommended: 3 NRTIs, 2 NRTIs plus 1 NNRTI and 2 NRTIs plus 1 PI.

- In 2003, WHO issued revised guidelines, reducing the number of recommended first-line treatments to four combinations of the same type, 2 NRTIs plus 1 NRT. At the same time, it incorporated stavudine-based combinations and the use of efavirenz, another NNRTI. PIs were also excluded from first-line treatments in the 2003 guidelines.

- In 2006, WHO released a second revision of HIV/AIDS treatment guidelines that included 16 standard regimens and 8 additional alternative regimens, almost all of which utilized 2 NRTIs plus 1 NRTI. This revision incorporated two new NRTIs, emtricitabine and tenofovir. The 2006 guidelines also suggested starting moving away from d4T-based regimens due to related toxicities.

- The latest WHO revision was released in 2010, and it reduced the number of recommended first-line treatments to just six combinations, excluding stavudine-based treatments.

Changes in treatment guidelines add complexity to developing a useful measure for capturing the progress that is made toward universal access to ART.[30] Targets need to be periodically updated to incorporate the latest recommendations and ART programmes must be systematically reviewed so they are aligned with the revised targets. This complication must be taken into account when evaluating the

**29** Waning et al. (2010). "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**30** Universal access is often taken to mean meeting a target of 80% of ART coverage. See 32 "Concept of universal access", Thieren (WHO, 2005).

degree of success in achieving universal access, because it can create difficulties in developing standardised criteria for measuring improvements.

A good example of this is the extensive use of stavudine in first-line treatments for HIV/AIDS in developing countries still today. Stavudine was one of the drugs recommended in the WHO guidelines until the 2006 guidelines were released, at which point its use was discouraged. Most recently, it was excluded from the guidelines in 2010. Stavudine was the first of its class to lose patent protection, which led to it becoming available at heavily discounted prices. For most of the past decade, large-scale ART programmes favoured extensive use of stavudine-based treatments as a cost-effective strategy. When concerns regarding stavudine's toxicity were recognised it was made clear that other treatment alternatives should be preferred, however, while developed countries had the capacity to switch to better, more expensive alternatives, the treatment programmes in many developing countries were unable to make similar changes.

### 2.2.2 The measurement of access to ART

The most widely used measure of access is the ART coverage rate, which is the indicator currently recommended by the United Nations General Assembly Special Session on HIV/AIDS (UNGASS).[31] This is the fraction of people eligible for ART that receive effective treatment. ART coverage rates provide an informative perspective on the relative position of countries in their pursuits of universal access as well as the changes in each country over time.

However, the measure provides an incomplete representation of the true level of access to ART and it is highly dependent on each country's definition of need for treatment:

- ART can include a wide variety of combinations of ARV drugs, but HIV/AIDS patients may need to receive specific combinations due to particular tolerability profiles or because they have developed resistance to earlier treatment combinations. Having access to the wrong combination of ARV drugs may be as ineffective as not having any access at all. The goal of universal access is probably better formulated as universal access to appropriate ART.

- Whether an HIV/AIDS patient should be started on ART is typically assessed by looking primarily at the CD4 cell count. The threshold below which ART should be initiated is established by treatment guidelines. The previous threshold of 200 cells/mm$^3$ was raised to 350 cells/mm$^3$ by the WHO in the 2010 HIV/AIDS guidelines, meaning that ART is now recommended to be initiated at an earlier stage of the disease. The immediate consequence of the change has been an increase in the number of people eligible for ART and as a result, ART coverage rates (compared to reported figures in previous years) have fallen even as more people are initiated on treatment.

- The CD4 cell count at which ART is initiated has an impact on the success of treatment to reduce morbidity and avoid mortality. Early initiation on ART after the CD4 cell count falls below the relevant threshold is an important dimension of universal access to ART.

- Continuity and adherence to treatment is a necessary condition to ensure efficacy and minimise the likelihood of developing resistance to treatments. Adequate monitoring and support

**31** Johnson and Boulle (2011), "How should access to antiretroviral treatment be measured?", Bulletin of the WHO, 89: 157-160.

of patients receiving ART is therefore also a component of effective access to ART that is not taken into account by ART coverage rates.

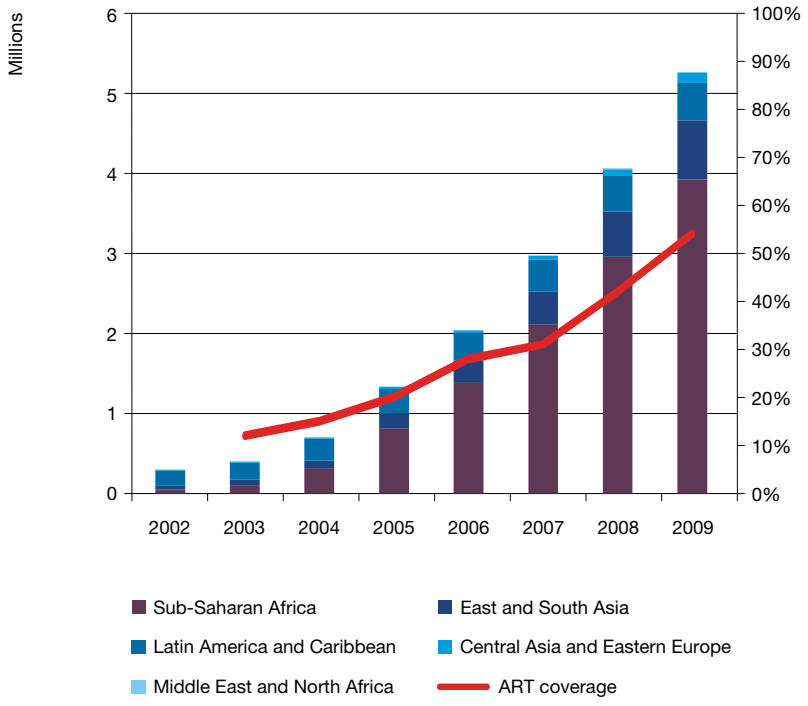
ART coverage rates remain the most commonly used measure to evaluate the achievements in improving access to ART, but need to be complemented by other measures that take into account all of the dimensions of access.

### 2.2.3 General improvement in ART coverage rates

Access to ART in developing countries, measured by coverage rates, has increased considerably between 2000 and 2009. Figure 16 depicts the evolution of the total number of people receiving ART in developing countries and the coverage rate according to the old WHO threshold for ART initiation (CD4 cell count <200 cells/mm$^3$). Starting from 1990 when less than 10% of people eligible for ART in developing countries effectively received it, the same indicator shows that in 2009 more than half of the population in need of ART has access to it today, which represents an estimated 5 million people.

Figure 16: *Patients receiving ART in developing countries by region*

SOURCE: BASED ON WHO PROGRESS REPORT 2010 AND WHO DATA (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




However, while this represents significant progress, it is important to note that this falls well short of achieving the target of universal access to ART which is usually defined as an ART coverage rate greater than 80%. The figures are even less positive if we were to measure ART coverage using the new WHO recommended

threshold for ART initiation (CD4 cell count <350 cells/mm$^3$). The change in the threshold, which recommends that ART is initiated at an earlier stage of disease, would increase the number of eligible patients in low- and middle-income countries by 45%, from 10.1 million to 14.6 million in 2009. This change reduces the ART coverage to only 36% of the patients in need of antiretroviral therapy in low- and middle-income countries.[32]

By far the largest proportion of people receiving ART in developing countries live in sub-Saharan Africa, where there is also the largest population of people infected with HIV. The region has received special attention from the international community due to the magnitude of its HIV/AIDS epidemic, its generalised pattern and the concentration of low-income countries in the region. As reflected in Figure 17, SSA achieved coverage rates close to 60% in 2009, above the average coverage rate of the developing world. This figure, however, hides the wide variation that exists between countries in the area. Eastern and Southern Africa have fared well, in part because of some particularly successful countries like Botswana, while Central and Western African countries have been much less successful at providing access to ART.

Botswana is one of the countries in the region that began offering universal treatment for patients with HIV/AIDS relatively early, in 2001. As a result of this, the number of patients with HIV/AIDS who receive ART has increased by a factor of four between 2000 and 2005. By 2009, 87% of the population in need of treatment was able to receive it.[33] The expansion of treatment was possible due to the expansion of treatment sites and to the increasing availability of medicines.

Rwanda has one of the highest rates of ART coverage of any country in Africa, at almost 90% by the newest WHO guidelines. Early efforts to curb the epidemic focused on prevention and education, and as of 2003, there were only seven sites that provided ARV treatment to the public. Since then, there have been several initiatives to increase access, and they have been very successful at achieving high coverage rates. It is important to recognise that while the coverage rates are quite high, the number of people receiving ART is only 80,000.[34] While this is a significant improvement from the 7,000 people who were receiving treatment in 2004, the relatively small total population allowed the ART coverage rates to ramp up quickly, which would have been a much slower process in a larger country such as South Africa.

In fact, South Africa has the largest ART programme in the world, but it also has the largest population of people with HIV/AIDS. As a result, access to treatment remains relatively low compared to other middle-income countries: 66% of people needing treatment actually received it in 2009 according to 2006 WHO guidelines (37% according to 2010 WHO guidelines).

**32** Chapter 4 in "Towards universal access. WHO Progress Report 2010" provides additional detail on the change in guidelines.
**33** Based on WHO data (extracted from http://www.aidsinfoonline.org/)
**34** Based on WHO data (extracted from http://www.aidsinfoonline.org/)

Figure 17: *Patients needing and receiving ART in sub-Saharan Africa*

SOURCE: WHO DATA (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

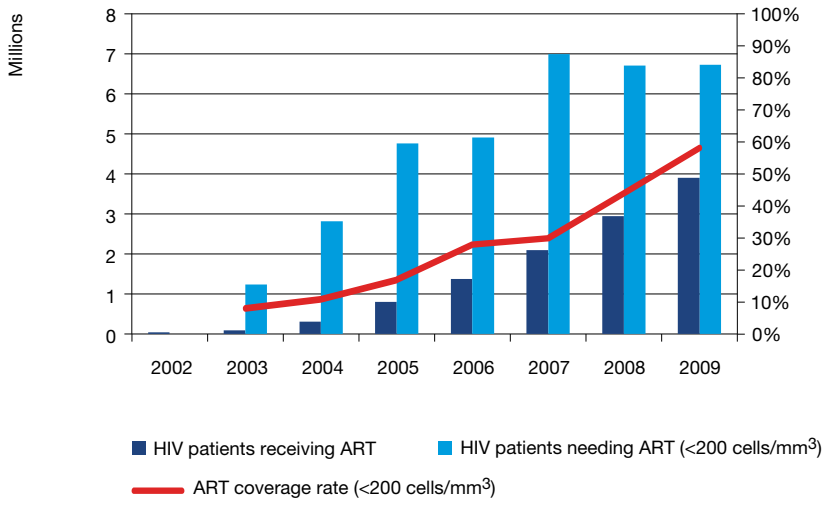



Figure 18: *Patients needing and receiving ART in South and East Asia*

SOURCE: WHO DATA (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

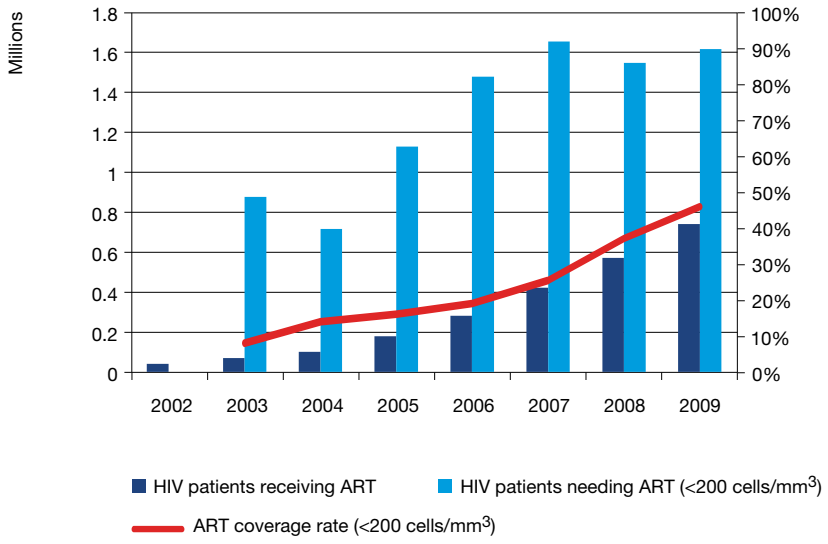
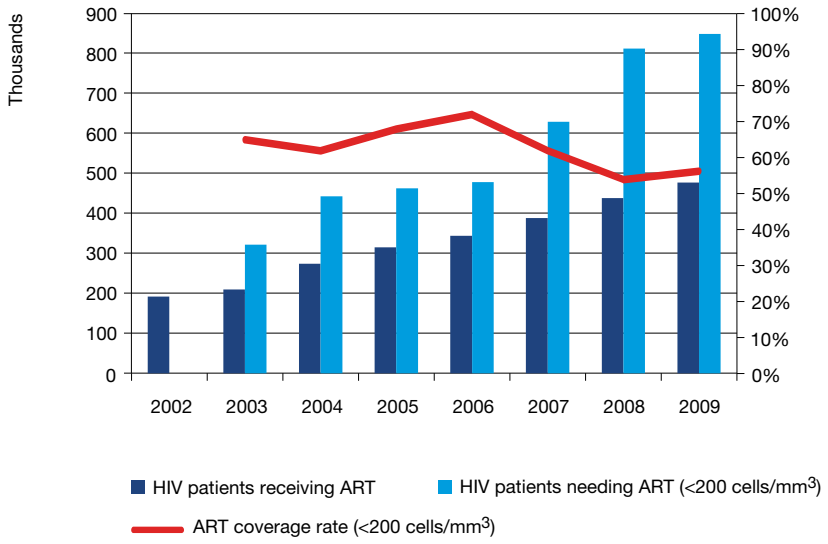


Figure 19: *Patients needing and receiving ART in Central and South America*

SOURCE: WHO DATA (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




Coverage rate have also improved in East and South Asia, although less so than in sub-Saharan Africa, and their coverage rates in 2009 were still below 50%.[35] This is likely to be a result of the later implementation of large-scale ART programmes. It is important to also take into account that HIV/AIDS is a concentrated epidemic in Asia, with much lower prevalence rates than in sub-Saharan Africa, where the magnitude of the epidemic made it a larger political priority.

Latin America has been a unique case, with high coverage rates already having been achieved by the late 90s and early 2000s. Although the number of patients receiving ART has continued to increase during the last decade, coverage rates have been relatively stable. The downward slope of the coverage rate in Figure 19 is due to an increase in the estimated number of people needing ART, not as a result of an absolute decrease in the number of people receiving ART.

Brazil provides a good example of this effect. Coverage rates in Brazil have indeed been stable between 80% and 85% from 2004 to 2009, the period for which the WHO provides records. High levels of ART coverage had largely been achieved by the end of the 90s as a result of the government's commitment to offer universal access to ART through public financing. Although we do not have the ART coverage rate for the period prior to 2004, the number of Brazilian HIV/AIDS patients receiving ART was already around 90,000 in 2000, which represented 23% of the total HIV-infected population in Brazil at that time. Given that only a fraction of HIV-infected people do need to be on ART, this figure is relatively high and implies that coverage at that time was already high in Brazil. By 2009, the same figure was 31%, with 200,000 HIV/AIDS patients receiving ART and a coverage rate of 80% according to the 2006 WHO guidelines.[36]

**35** Based on WHO data (extracted from http://www.aidsinfoonline.org/)
**36** Based on WHO data (extracted from http://www.aidsinfoonline.org/)

Although Brazil has clearly achieved high levels of ART coverage, it has been unable to attain the levels of coverage observed in the best-performing developing countries. In the South American region in particular, both Argentina and Chile achieved higher levels of coverage than Brazil did in 2009, irrespective of whether we use the 2006 or 2010 WHO guidelines to compute ART coverage rates.

The vast geography of Brazil, the unequal economic development of Brazilian regions and the uneven distribution of people living with HIV/AIDS across the country have combined to shape the geographic distribution of healthcare facilities that provide HIV/AIDS treatment and care. These facilities are concentrated in the large metropolitan regions of the South and South-east, especially along the Rio de Janeiro–Sao Paulo corridor. The lack of centres in some regions may act as a barrier against access to ART.

In Mexico, the number of HIV/AIDS patients receiving ART has increased steadily over the last decade. The figure has evolved from 7,000 patients being treated in 1997 to 60,000 patients receiving ART in 2009. According to data from the Mexican National Centre for HIV/AIDS Prevention and Control (CENSIDA), universal coverage of diagnosed HIV/AIDS patients was achieved by 2003. However, this was a result of the large number of undiagnosed people; the estimated number of people needing ART in Mexico is substantially larger than the number of diagnosed patients needing ART.

According to the WHO estimates of the number of patients needing ART in Mexico, ART coverage rates have increased steadily in Mexico over the period 2004-2009. By 2009, Mexico was able to offer ART coverage to 71% of HIV/AIDS patients with a cell-count below 200 cells/mm$^3$ and to 54% of patients with cell counts below 350 cells/mm$^3$.[37]

Although Mexico has undoubtedly been successful at increasing access to ART, universal access remains an unmet goal, in large part because of the substantial number of undiagnosed HIV infected people.

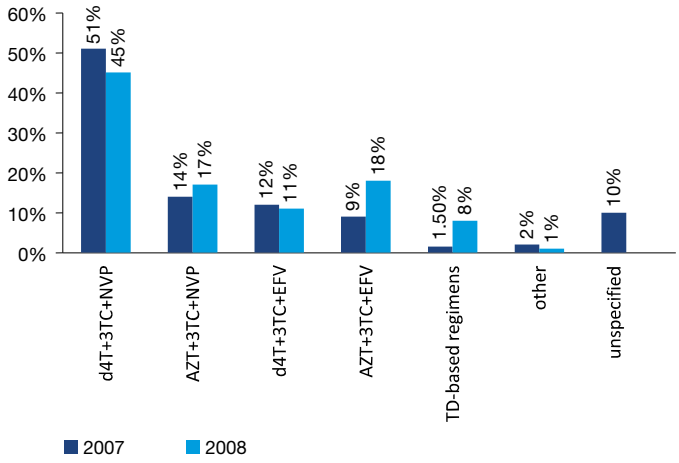
### 2.2.4 Access to newer ARV drugs

There is limited data on how access to different generations of ARV medicines has evolved over time. Successive revisions of the WHO guidelines for HIV/AIDS have resulted in significant variations in the number and composition of recommended first-line regimens. This has been reflected in corresponding swings in relative volumes purchased of different ARV drugs.[38] Figure 20 shows the share of patients that were treated with alternative first-line treatments in 2007 and 2008. The share of patients that were given stavudine-based regimens in developing countries was 6 points lower in 2008 than one year before. On the other hand, the share of patients taking zidovudine-based regimens was 9 points higher in 2008, while the share of patients being treated with tenofovir-based was 6.5 points higher. These changes took place in just one year and reflect the impact of treatment guidelines on purchasing and prescribing decisions.

**37** Based on WHO data (extracted from http://www.aidsinfoonline.org/)
**38** Waning et al. (2010). "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).

Figure 20: *Share of patients on each ART treatment in 2007 and 2008*

SOURCE: WHO PROGRESS REPORTS 2008 AND 2009




An important number of low- and middle-income countries have already incorporated into their national treatment guidelines the 2010 WHO recommendations on eligibility criteria and treatment. According to the WHO Progress Report 2010, in a subset of 54 countries that participated in the study, 45 had already recommended initiation of antiretroviral therapy for patients with CD4 counts at or below 350 cells/mm$^3$ and 33 are actively shifting from stavudine-based to regimens containing zidovudine or tenofovir.[39]

However, a majority of HIV/AIDS patients continue to be treated with stavudine-based regimens, in spite of their toxicity and the recommendations of the WHO against their use. While these regimens are no longer prescribed in developed countries, the shift to newer regimens is proving to require more time in developing countries.

Again, regional differences are relevant in terms of the composition of ART regimens. As Table 4 shows, the use of stavudine as a first-line treatment was much lower in Latin America than in other developing countries. Instead, zidovudine- and tenofovir-based regimens represent a higher proportion of first-line treatments in Latin America.

**39** Towards universal access. WHO Progress Report 2010, pp. 69.

Table 4: *ARV use per drug in low- and middle-income countries in 2009*

REGIMENS MAY CONTAIN MORE THAN ONE DRUG OF THE SAME CLASS
SOURCE: TOWARDS UNIVERSAL ACCESS WHO PROGRESS REPORT 2010, TABLE 4.8, PP. 66.

| | | 59 low - and middle - income countries (excluding countries from the Americas region) | | 17 countries in the Americas region | |
|---|---|---|---|---|---|
| Antiretroviral medicines* | | Proportion of first-line combinations containing the drug (%) | Proportion of second-line combinations containing the drug (%) | Proportion of first-line combinations containing the drug (%) | Proportion of second-line combinations containing the drug (%) |
| NRTI | 3TC | 94.2 | 31.6 | 91.1 | 75.0 |
| | d4T | 59.7 | 3.0 | 2.3 | 30.3 |
| | AZT | 32.1 | 47.2 | 71.3 | 27.8 |
| | TDF | 7.7 | 32.4 | 21.4 | 17.3 |
| | ABC | 0.4 | 22.3 | 4.0 | 14.0 |
| | ddI | 0.3 | 48.1 | 0.8 | 17.3 |
| | FTC | 5.4 | 15.5 | 7.9 | 2.6 |
| NNRTI | NVP | 60.7 | 1.1 | 12.4 | 5.1 |
| | EFV | 38.5 | 1.6 | 50.2 | 20.1 |
| | ETV | 0.0 | 0.0 | 0.0 | 0.0 |
| Protease Inhibitors | LPV | 0.4 | 92.7 | 20.9 | 37.9 |
| | NFV | 0.0 | 0.3 | 0.0 | 0.1 |
| | IDV | 0.1 | 0.9 | 0.0 | 5.9 |
| | SQV | 0.0 | 0.3 | 3.0 | 1.9 |
| | ATV | 0.0 | 0.0 | 12.3 | 17.7 |
| | FPV | 0.0 | 0.0 | 0.1 | 2.9 |

In the context of the analysis of the case studies, we attempted to obtain more detailed data on the usage of different ARVs in each country. We were however unable to find systematic data.

## 2.2.5 Prices of ARV drugs

The prices of ARV drugs vary substantially across active principles and across countries. Table 5 shows the prices of several first-line combined therapies recommended by the WHO guidelines during the last ten years in low-, lower middle-, and upper middle-income countries. In general, newer drugs tend to have higher prices than older drugs, and the prices of all drugs are positively correlated with the level of income of the country where they are sold.

Table 5: *ARV prices per therapy in low- and middle-income countries in 2009*

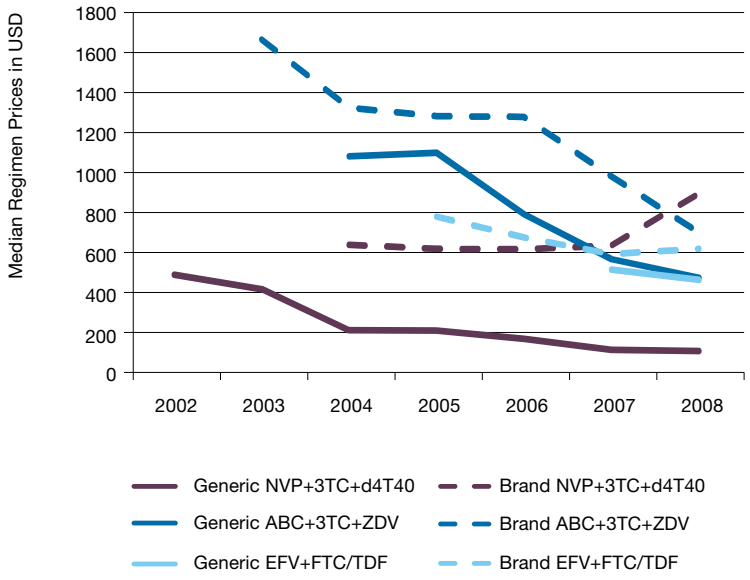
*PRICE/PERSON/YEAR CALCULATED USING THE LEAST EXPENSIVE ARV'S TO CREATE EACH REGIMEN
SOURCE: WANING ET AL. (2010)

| | | Median (25th, 75th percentile) Regimen Prices* in USD | | |
|---|---|---|---|---|
| | ART | Low Income | Lower-Middle Income | Upper-Middle Income |
| Old First-Line Regimens from 2003 WHO Guidelines: | 3TC/NVP/d4T30 | 88 (83, 90) | 87 (50,151) | 110 (84, 222) |
| | EFV+3TC/d4T30 | 198 (183, 233) | 147 (52, 253) | 211 (172, 235) |
| | 3TC/NVP/ZDV | 154 (144, 162) | 172 (154, 259) | 161 (161, 189) |
| | EFV+3TC/ZDV | 260 (246, 286) | 216 (118, 298) | 326 (260, 370) |
| | 3TC_NVP+TDF | 244 (266, 278) | 256 (244, 288) | 387 (311, 591) |
| | EFV+3TC+TDF | 349 (321, 399) | 301 (207, 392) | 477 (404, 527) |
| New First-Line Regimes from 2006, 2009 WHO Guidelines: | FTC/TDF/NVP | 361 (325, 366) | 399 (292, 427) | 525 (368, 726) |
| | EFV+FTC/TDF | 465 (419, 487) | 443 (256, 531) | 616 (461, 663) |
| | ABC+3TC+NVP | 398 (361, 450) | 418 (392, 457) | 491 (443, 705) |
| | ABC+EFV+3TC | 203 (455, 571) | 463 (355, 561) | 581 (536, 641) |

A general trend during the last decade has been for the prices of ARV drugs to decrease. Where generics have been available, the prices of those generics have been substantially lower than the price of corresponding branded products, and both branded and generic prices have declined over time. This is shown in Figure 21 for three first-line ART combinations.

Figure 21: *Evolution of branded and generic prices of selected ARV combinations*

SOURCE: CRA USING DATA FROM WANING ET AL. (2010)




## 2.2.6 Patient surveillance and adherence to ART

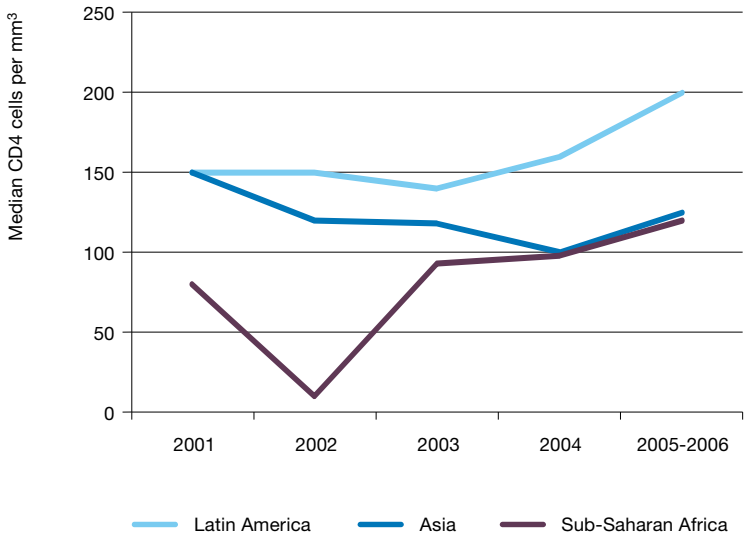
It has become widely recognised that timely initiation of patients onto ART is an important factor in reducing morbidity and avoiding mortality. Though the most recent WHO guidelines recommend starting treatment when HIV/AIDS patients have a CD4 cell count below 350 cells/mm$^3$, at the start of the last decade, ART was considered by most people to only be required by HIV/AIDS patients with a CD4 cell count below 200 cells/mm$^3$. The result was that in most cases patients were not initiated on ART until the disease was at an advanced stage. Many patients in the developing world still access ART only when they are already presenting significant clinical symptoms, with the majority experiencing severe immune suppression (CD4 count below 100 cells/mm$^3$).[40]

Figure 22 shows the median CD4 cell count of patients starting ART during the first half of the 2000s. Late initiation in ART is often caused by suboptimal testing and diagnosis. A significant number of people living with HIV are not aware of their status and only get access to ART once they start developing external symptoms of the disease, which usually doesn't happen until patients reach very low CD4 cell counts.

**40** Girard et al. (2010), "Universal Access in the Fight Against HIV/AIDS", Science, 329: 147-149.

Figure 22: *CD4 cell count at ART initiation*

SOURCE: WHO PROGRESS REPORT 2009




In South Africa, for instance, it is estimated that delays in initiating treatment mean that the average starting point for ART is approximately 87 cells/mm$^3$. A study in two clinics found that as many as 60% of new patients receiving testing already had counts below 200 cells/mm$^3$. Of those patients, only 42% began treatments within the following twelve months, and more than 20% were known to have died, 82% of whom died before ever receiving ART.

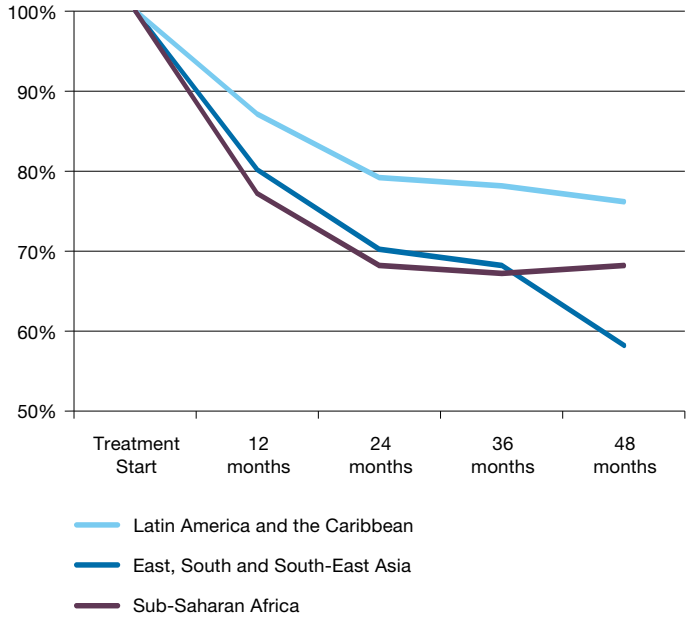
In Mexico, the average cell-count for patients initiating ART in Mexico was 90 cells/mm$^3$, which is similar to the average observed in some SSA countries. Mexican patients get access to treatment when the disease is already at an excessively advanced stage, which limits their capacity to benefit from the treatment.

Adherence to and retention of patients on ART is also important to ensure the efficacy of the treatment. ART is a lifelong treatment and as a result, it requires appropriate monitoring of patients using a long-term perspective. This surveillance requires adequate access to healthcare and counselling for patients on ART. As shown in Figure 23, currently around 20% of patients abandon ART one year after initiation, and around 30% of patients by the end of three years.[41] There is also evidence that shows wide variation across countries. For example, in Botswana, treatment adherence has been very strong, with greater than 90% of people on treatment 12 months after initiation in 2009, well above the average for sub-Saharan Africa.[42]

**41** Towards universal access. WHO Progress Report 2010. Fig. 4.5.
**42** UNAIDS database (extracted from http://www.aidsinfoonline.org/)

Figure 23: *Retention on ART in 2008*

SOURCE: TOWARDS UNIVERSAL ACCESS. WHO PROGRESS REPORT 2009. FIG. 4.5.




## 2.2.7 ART as a prevention strategy

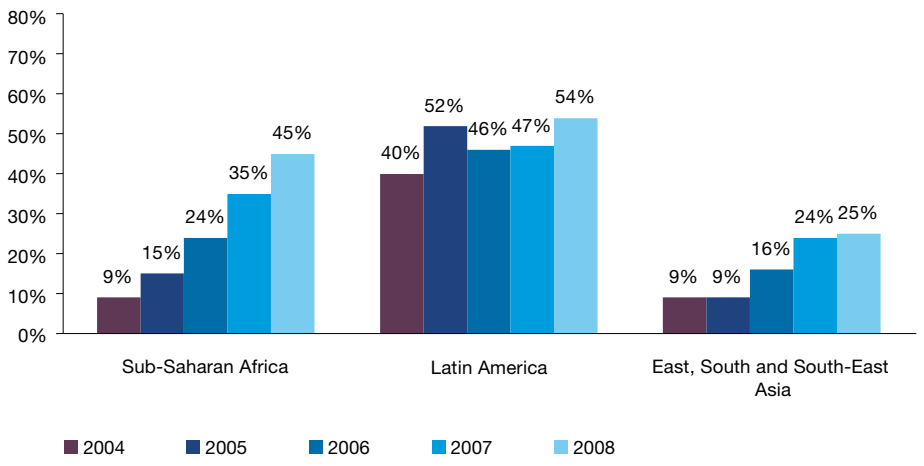
ART is increasingly viewed not only as a treatment for AIDS, but also as a means of preventing HIV transmission. The crucial role of ART in the prevention of mother-to-child transmission (PMTC) has been well established. In 2009, an estimated 370,000 children contracted HIV during the perinatal or breastfeeding period, down from 500,000 in 2001, largely thanks to the use of PMTC ARV treatment. In some countries like South Africa, coverage for PMTC has reached 90%, and transmission has been drastically reduced as a result.

However, HIV continues to weigh heavily on maternal and child mortality in some countries. In 2009, UNAIDS called for the virtual elimination of mother-to-child transmission of HIV by 2015, considering it a realistic goal even in the most severely affected countries, provided that further action is implemented.[43] Figure 24 shows the improvement in ART coverage for PMTC between 2004 and 2008. Even in Latin America, where ART coverage is relatively high, levels of PMTC coverage are barely above 50%. Coverage has improved both in SSA and Asia, but it remains low, especially in Asia.

**43** "UNAIDS REPORT ON THE GLOBAL AIDS EPIDEMIC 2010"
available at http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf

Figure 24: *Share of pregnant women living with HIV receiving ART for PMTC*

SOURCE: TOWARDS UNIVERSAL ACCESS. WHO PROGRESS REPORT 2009. FIG. 5.5.




Recent research has confirmed the important role of ART in preventing HIV transmission within sero-discordant couples.[44] The most recently published results of the HPTN 052 study show that antiretroviral therapy is highly effective for preventing transmission of HIV in sero-discordant couples between whom the index case has CD4 cell counts of 350-550 cells/mm$^3$.[45]

The effectiveness of ART as a tool for preventing HIV transmission may call for an expansion of treatment to HIV-infected populations that are currently deemed not eligible for treatment. The increase in the number of patients eligible for treatment would have an impact on coverage rates, like the increase of the threshold for treatment initiation has already had, but it also has the potential to greatly enhance prevention efforts.

As a result, programmes to expand access to ART also constitute an important element of the strategy to prevent HIV transmission. This furthers the need for integrated responses to the HIV/AIDS epidemic that account for the interactions between treatment and prevention efforts.

## 2.3 SUMMARY

The HIV/AIDS epidemic shows distinct patterns of evolution across different regions of the developing world. The largest proportion of people with HIV lives in sub-Saharan Africa, where the epidemic affects the entire population. In other developing regions, where levels of HIV prevalence are much lower, the epidemic is concentrated in vulnerable populations, primarily sex workers, men who have sex with men and injecting drug users.

Latin American countries have been more successful at containing the growth in the number of people living with HIV than countries in SSA and Asia.

**44** Girard et al. (2010), "Universal Access in the Fight Against HIV/AIDS", Science, 329: 147-149.
**45** Schwartlaender et al. (2011), "Towards an improved investment approach for an effective response to HIV/AIDS", Lancet 377: 2031-41.

Latin America achieved relatively high levels of access to ART by the late 90s, compared with much lower access at that time in other developing regions. In SSA and Asia, ART coverage rates have only increased since the beginning of the last decade.

The goal of universal access has not yet been achieved, despite the relative success observed in scaling-up ART programmes. Almost every developing country has substantially improved access to ART (although the changes in coverage definitions require care to be taken when comparing rates over time), but still only about half of the HIV-infected persons eligible for ART are receiving it in developing countries. Complementary indicators of access, like the CD4 cell count at initiation of the treatment and the access to newer ARV drugs, show the same evolution over the last decade: significant improvement but falling short of reaching universal access.

# 3

# A DECADE OF EFFORTS TO IMPROVE ACCESS TO ART

In this chapter, we examine the different types of interventions that have been used to address these barriers[46], how they have been funded and the role of different stakeholders in these interventions.

## 3.1 WHAT HAS BEEN DONE TO ADDRESS THE BARRIERS TO UNIVERSAL ACCESS

We propose the following categorisation of interventions and discuss in turn how each of these has contributed to overcoming barriers that hinder access to ART:

- Political prioritisation;
- Financial resources devoted to International funding for the purchasing of ARV drugs;
- Pricing of ARVs;
- Voluntary licensing and non-assertion of intellectual property rights and the role of generics;
- Compulsory licensing and other TRIPS flexibilities;
- Development of purchasing mechanisms;
- Capacity building;
- Programmes to overcome stigma; and
- Partnerships.

### 3.1.1 Political prioritisation

A lack of political commitment from local authorities is often identified as a key barrier. In order to improve access to ART requires a wide range of interventions to be coordinated and implemented in parallel, which needs the leadership of local stakeholders, foremost of which are national governments.

A fundamental change in terms of political commitment was of course the adoption of universal access to ART as a political priority by the whole international community and most national governments in developing countries. This political commitment, represented by the inclusion of access to HIV/AIDS treatment among the UN Millennium Development Goals, was the prelude of the series of interventions implemented in the subsequent years.

The mobilisation of donors began after UN Secretary-General Kofi Annan's call for a "war chest" to fight the epidemic: *"AIDS has become not only the primary cause of death on this continent, but our biggest development challenge. And that is why I have made the battle against it my personal priority".*

Kofi Annan identified priority areas as prevention, reducing transmission from mother to child through access to ARVs, providing universal access to treatment, continued innovation in HIV/AIDS treatments and a focus on the most vulnerable populations. The UN Millennium Development Goals led to a significant increase

**46** Some of these were system-level barriers, like the availability of healthcare facilities or financial resources, while others were population-level barriers such as the lack of awareness about ART or the stigmas associated with HIV/AIDS. Posse et al. (2008), "Barriers to access to antiretroviral treatment in developing countries: a review", Tropical Medicine and International Health, 13(7): 904-913.

in international effort to provide care and treatment to the poorest countries in the world.[47] Kofi Annan's vision included a role for the innovator pharmaceutical industry: *"The world's biggest pharmaceutical companies... accept the need to combine incentives for research with access to medication for the poor. They are ready to sell drugs to those countries at greatly reduced prices".*

It also included a role for generic medicines and a flexible approach toward intellectual property laws in the poorest countries. *"This crisis is so grave that developing countries must face it by exploiting all options to the full — including the production and importation of «generic» drugs under licence, within the terms of international trade agreements".*

The results of this increased political will at the global level are clear. In short order, the Global Fund to Fight AIDS, Tuberculosis and Malaria was created in 2002, followed by the US Government-led President's Emergency Plan for AIDS Relief in 2003.

Equally or more important than the political will of the global community is the political will at the local level. The role of the NGOs in battling HIV/AIDS should not be understated.[48] NGOs have been especially active in the poorest countries, identifying problems, raising awareness, funding ARV programmes and providing access to ART. For example, in 2000, Médecins Sans Frontières (MSF) began providing ART for HIV/AIDS in Thailand, Cameroon and South Africa to a limited number of people in urgent need of treatment.[49] Initially MSF was only involved in the provision of treatment for dedicated HIV/AIDS projects, but over time MSF has increasingly decentralised HIV services into primary healthcare facilities and partnered with local health ministries to deliver care.

It is clear that the result of this varied significantly from country to country. In some countries HIV was a significant political priority from the beginning of the decade. This was clearly the case in Brazil and Botswana. In other countries political priority only occurred later, such as in Rwanda and especially in South Africa. We look in more detail at these cases in Chapter 4.

### 3.1.2 Financial resources devoted to purchasing of ARV drugs

Lack of financial resources to fund universal access to ART was clearly one of the barriers to greater access at the beginning of the decade. However, developing countries are diverse with respect to their relative wealth. Middle income countries have been able to develop large-scale ART programmes relying mainly on their own financial resources, with minimal foreign funding. This is not the case for low-income countries, which clearly needed substantial contributions from the international community to be able to scale-up their ART programmes.

During the majority of the 90s, the limited resources available to fight the HIV/AIDS epidemic in developing countries led to a focus on prevention over treatment. International donors promoted this focus by primarily offering funding for prevention programmes rather than for treatment programmes. However, the debate on funding prevention versus treatment gradually evolved towards a more balanced approach. The international AIDS conference that was held in

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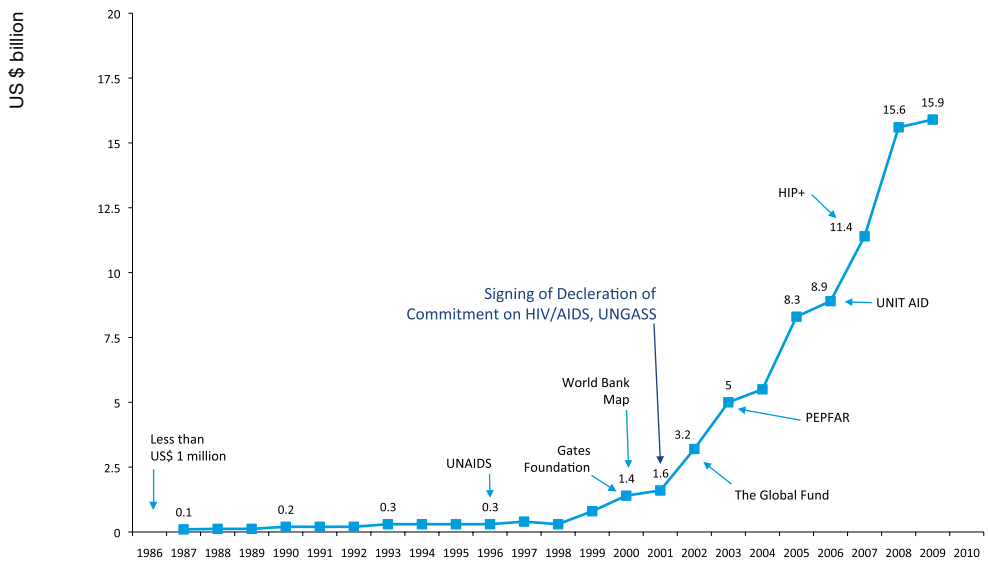
**47** Address by Kofi Annan to the African Summit on HIV/AIDS, Tuberculosis and Other Infectious Diseases. 26 April 2001
**48** "The politics of national HIV/AIDS responses: a synthesis of literature" Clare Dickinson March 2006.
**49** "GETTING AHEAD OF THE WAVE: Lessons for the Next Decade of the AIDS Response" MSF May 2011

Spain in 2002 heralded a new and comprehensive approach to combating HIV/AIDS. This included wide-scale prevention and treatment programmes, which would be made possible by better treatments that would be practical to implement even in low-income countries, because of increased funding and decreasing drug costs. While the balance between prevention and treatment remains a challenging question in resource-constrained settings, since then, there has been a shared international commitment to support large-scale ART programmes in developing countries.[50]

Domestic and international aid to control HIV/AIDS in developing countries has risen dramatically during the last decade, both from bilateral and multilateral organisations. Figure 25 shows the evolution of resources available for fighting HIV/AIDS in developing countries between 1986 and 2010. It remained low during the 90s, before exploding over the last decade, especially since the Declaration of Commitment on HIV/AIDS. The timing of the main multilateral initiatives is represented in this figure, including the formation of UNAIDS, the Global Fund, PEPFAR and UNITAID.

Figure 25: *Resources availability for HIV in low- and middle-income countries*

SOURCE: UNAIDS



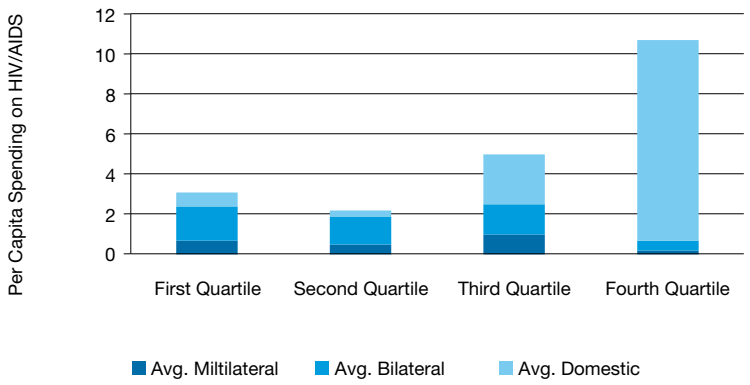

50 Morrison and Summers (2003), "United to Fight HIV/AIDS?", The Washington Quarterly, 26: 177-193.

More than half of the $16 billion that was spent fighting HIV/AIDS in 2009 came from domestic sources in low- and middle-income countries, primarily from public spending. Foreign governments' funding amounted to $7.6 billion in 2009, including both bilateral and multilateral aid. Three quarters of this international funding was provided as bilateral aid, while the rest was distributed through multilateral organisations, like the Global Fund and UNITAID. The US government is the largest donor, accounting for more than one quarter of all resources available for HIV/AIDS. The US distributes almost 90% of its aid bilaterally through its own programme, PEPFAR.[51]

Aid from international donors has played a pivotal role in providing the necessary funds to establish large-scale ART programmes in low-income countries. In 2009, low-income countries received 78% of all international donations for HIV/AIDS, while lower middle-income countries received 14%. As would be expected, each country's degree of dependence on international aid for ART financing is negatively correlated with that beneficiary's income per capita.[52] Figure 26 shows the breakdown of HIV/AIDS spending per capita in countries with different levels of per capita income. International aid accounted for more than three quarters of the total spending on HIV/AIDS in the 25% of developing countries with the lowest levels of income. At the other end of the spectrum, developing countries with the highest levels of income relied almost exclusively on domestic resources to finance their response to the epidemic.

Figure 26: *HIV/AIDS spending by income quartile*

SOURCE: PEIFFER AND BOSSALIS (2010)




**51** Global Report (2010)
**52** Peiffer and Boussalis (2010), "Foreign Assistance and the Struggle Against HIV/AIDS in the Developing World", Journal of Development Studies, 46(3): 556-573.

While international aid has allowed low-income countries to scale-up their spending on HIV/AIDS, it has not eliminated the differences in the level of spending per capita in countries with different levels of income. Absolute spending on HIV/AIDS per capita is positively correlated with the level of income, and middle-income countries appear to have been able to sustain these higher levels of spending without relying significantly on international funding. It is not surprising that lack of financial capacity affects primarily low-income countries and that international aid has been oriented to ease these financial constraints.

International aid for HIV/AIDS is not exclusively based around financing ART, it is also used to sustain prevention programmes, build capacity and improve logistical activities. There is clear evidence of the positive effects of international aid on access in those countries that have received it. It has been estimated that a one dollar increase in HIV foreign aid per capita increases the odds of complete ART and pregnant ART coverage by between 3-5%.[53] This suggests that financial constraints were indeed a significant barrier to access in low-income countries and that international aid has played an important role in overcoming this barrier.

### 3.1.3 Pricing of ARVs

Alongside limited financial resources, the prices of ARV drugs when they were first launched onto the market also constituted a potential barrier to increasing access to ART in resource-constrained settings, and in some cases it called into question the cost-effectiveness of ART in these settings. This was a central issue in the debate that occurred during the 90s about prevention-based strategies versus treatment-based strategies in the fight against the HIV/AIDS epidemic, which were often viewed as being alternative approaches. The lack of affordability of treatment-based strategies in developing countries is often held responsible for the late adoption of ART in many developing countries, with the notable exception of Brazil.

There has been increasing consensus among stakeholders that the prices for ARV drugs should be different in low-, middle- and high-income countries to account for differences in their ability to pay for drugs. Differential pricing[54] mechanisms have been promoted by the WHO and adopted by most innovator pharmaceutical companies to allow low- and middle-income countries to purchase essential drugs at discounted prices relative to the higher prices that are paid in more developed countries for in-patent drugs.[55] The aim of differential pricing is to reduce financial barriers to access for low-income countries while providing manufacturers with profit opportunities in richer markets so that incentives to innovate are preserved.[56]

One of the challenges stemming from the use of differential pricing is preventing the exportation of drugs sold at discounted prices to developed countries by distributors that engage in arbitrage practices. This has been a source of concern among innovator firms and has prompted the establishment of additional con-

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**53** Peiffer and Boussalis (2010), "Foreign Assistance and the Struggle Against HIV/AIDS in the Developing World", Journal of Development Studies, 46(3): 556-573.
**54** These are also referred to as tiered pricing, preferential pricing or equity pricing in the literature and by the companies. We use the term differential pricing throughout this report.
**55** The report "Developing World Health Partnerships Directory 2010" published by IFPMA provides a comprehensive view of initiatives undertaken by pharmaceutical companies, including differential pricing schemes for ARV drugs.
**56** WHO (2001),"More equitable pricing for essential drugs: What do we mean and what are the issues?"

trols in the supply chain. For example, companies have introduced identification logos for drugs that are sold at discounted priced in developing countries.[57]

Currently, most manufacturers of branded ARV drugs operate a mechanism to provide differential pricing for developing countries. Typically, low-income countries and countries with the most severe HIV/AIDS epidemics are offered branded ARV drugs at significant discounts and in some cases even at not-for-profit prices. Middle-income countries are typically excluded from the lowest prices, although they are often offered discounts relative to the prices paid in developed countries.[58]

While the optimal level of price differentiation that should be offered to low- and middle-income countries is a matter of discussion amongst stakeholders, not-for-profit pricing is generally considered the lower bound for the prices that are offered through this type of mechanism. Pricing below cost of production, while offered on occasion, would be considered a partial donation of drugs.

Based on a series of interviews with manufacturers of branded ARV drugs, we have identified broad support in the industry for the use of differential pricing schemes. In particular, not-for-profit pricing is seen as a reasonable approach in low-income countries that have to manage their HIV/AIDS epidemic with very limited financial resources. There is also agreement among branded manufacturers that while middle-income countries should be charged prices below those charged in high-income countries, they should contribute to rewarding innovation by paying prices that are above cost.

**Evidence on differential pricing schemes**

Based on interviews with pharmaceutical companies, existing industry[59] and NGO literature[60] we can observe that most companies are offering products on the basis of differential-pricing schemes. For example:

- Abbott makes its ARV drugs available in all 69 African and least developed countries at prices which are among the lowest for branded or generic protease inhibitors. Unlike most other international pharmaceutical companies, Abbott has chosen to supply at preferential terms to low-income markets rather than use licensing agreements to increase access.

- Boehringer Ingelheim charges a reduced (not-for-profit) price for all countries classified by the World Bank as low-income, all Least Developed Countries (LDCs) according to the UN definition, and for all countries in sub-Saharan Africa. In addition, all middle-income countries qualify for a lowered price.

- Bristol-Myers Squibb (BMS) provides all of its ARV drugs at not-for-profit prices in sub-Saharan Africa. A further reduction is applied in the price of paediatric formulations from not-for-profit to significantly below cost. BMS also implements a global differential pricing policy.

- Gilead has a differential pricing system for its ARV drugs, including tenofovir and emtricitabine+tenofovir, based on each country's economic status and HIV prevalence. It offers substantial price reductions in 130 countries.

- Merck & Co. operates a differential pricing policy whereby it provides its ARV drugs at not-for-profit prices in LDCs and those hardest hit by the HIV/AIDS epidemic. The offer ex-

**57** http://aidsmap.com/European-Union-underpins-tiered-pricing-for-HIV-TB-and-malaria-drugs/page/1415939/
**58** Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?", PLoS One, 2(3).
**59** "Developing World Health Partnerships Directory 2010". IFPMA (2010)
**60** http://utw.msfaccess.org/drugs/

tends to the governments of these countries, as well as to international donor agencies, non-governmental organisations (NGOs), charitable organisations and private-sector employers. Countries with a higher degree of economic development and lower prevalence rate receive a less discounted price.

- Roche supplies its HIV protease inhibitors at not-for-profit prices for people living in LDCs and in sub-Saharan Africa. In addition, Roche established significantly reduced pricing for some ARV drugs for low- and lower middle-income countries.

- ViiV Healthcare, which was formed jointly by GlaxoSmithKline and Pfizer, offers all of its ARV drugs at not-for-profit prices to public sector customers and not-for-profit organisations in all LDCs and all of sub-Saharan Africa. In addition, the Global Fund, PEPFAR and all private employers in SSA who provide care and treatment to their uninsured staff can purchase its ARVs at not-for-profit prices.

### 3.1.4 Voluntary licensing and non-assertion of intellectual property rights and the role of generics

The affordability of treatment is related to both financial resources and the cost of ARV drugs. There is a concern that protection of intellectual property rights has resulted in higher prices acting as a potential barrier to universal access to ART. Protection of intellectual property rights grants originator companies market exclusivity, preventing competition from generic producers until expiry of patents. This prevents price competition for patent-protected drugs, often even in developing countries. While differential pricing theoretically offers a way to ensure that prices in developed countries do not impede access to ARV in developing countries, an alternative strategy has been to allow generic supply of patented ARV drugs under certain circumstances.

The Doha Declaration on the TRIPS Agreement and Public Health establishes that LDCs have no obligation to enforce patents and data protection for pharmaceutical products until 2016.[61] Consequently, intellectual property rights per se cannot currently constitute a barrier to access to ART in these countries (at least until 2016).[62] However, LDCs typically lack the capacity to produce ARV drugs locally — so although in principle, intellectual property should not be a barrier in those countries, it can be in practice. This was the reasoning behind Paragraph 6, which is designed to allow generic manufacturers in other countries to provide generic supply in those cases.

To prevent this lack of production capacity from impeding access to ART, a number of pharmaceutical companies have voluntarily licensed their products to generic producers in third countries, allowing them to supply generic versions of the licensed products only in low-income countries.[63] This has been, for instance, the case with a number of Indian generic companies that currently supply a considerable share of ARV drugs consumed in low-income countries, especially in sub-Saharan Africa. Often, voluntary licensing is done with certain conditions,

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**61** http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm
**62** There are few least-developed countries which already have some form of IP protection in place before TRIPS. However, even when this is the case, these IP protections are not normally enforced.
**63** The following link provides an overview of the industry's approach to voluntary licensing and non assertion: http://www.ifpma.org/fileadmin/content/Innovation/IP%20and%20Access/20100728_Statement_VoluntaryLicensing_NonAssert_28July10.pdf

like a commitment to supply only countries where patents are non-asserted or non-enforced and to ensure some quality standards certified by the WHO through its Prequalification programme for generic producers. Voluntary licensing agreements (VLA) are frequently complemented by technology-transfer programmes to contribute building local production capacity.[64] Either through local production or through importation of generics from third countries, evidence confirms that generic versions of patented drugs are procured in large quantities in sub-Saharan Africa.[65]

Middle-income countries are in a different situation, as they must, in principle, enforce intellectual property rights for pharmaceutical products if they are subject to TRIPS (although the timing at which this occurred varies between countries as does their interpretation). Although some companies have chosen not to assert their patent rights in any country in sub-Saharan Africa, companies generally enforce their patents in middle-income countries, especially outside the sub-Saharan region. This has limited the availability of generic products for a number of in-patent ARV drugs in middle-income countries. However, in cases such as South Africa, some generic producers have been granted voluntary licences for the production of various ARV drugs.[66]

Particularly, in India, the existing intellectual property system has allowed Indian generic firms to become the largest suppliers of ARV drugs in low- and middle-income countries over the last decade.[67] There is considerable debate regarding how this might change in the future with greater enforcement of patents in accordance with international law.

Intellectual property rights may become more relevant as the use of second-line treatments increases in the coming years. At present, more than 95% of patients on treatment are on first-line antiretroviral medicines, some of which are off-patent. As drug resistance increases over time, more patients will require second- and third-generation medicines. It has been forecasted that 6-10% of patients will switch therapy per year.[68] Most of the more recent medicines will remain under patent protection for years to come.[69] To the extent that patents continue not to be asserted in relation to supplying low-income countries, no significant impact should be expected.

Second line drugs have been procured in lower quantities than first line drugs, even despite the non-enforcement of patent rights in low-income countries. Low volumes over which to spread fixed costs may explain in part why even generic prices for second line drugs remain higher than first line treatment.[70] Increasing demand for second-line ARV drugs may create incentives for increased generic entry, which could have a downward impact on prices.

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**64** http://www.ifpma.org/fileadmin/content/Innova-tion/IP%20and%20Access/20100728_Statement_VoluntaryLicensing_NonAssert_28July10.pdf
**65** Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?", PLoS One, 2(3).
**66** Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?", PLoS One, 2(3).
**67** Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?", PLoS One, 2(3).
**68** http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110531_JC2095E_aids_at_30_section1-5.pdf
**69** http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110531_JC2095E_aids_at_30_section1-5.pdf
**70** Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?", PLoS One, 2(3).

**Evidence on Voluntary Licensing and Technology Transfer**

Based on interviews with pharmaceutical companies and existing industry[71] and NGO literature[72] we can observe many companies offer voluntary licensing or don't assert patents. For example:

- Boehringer Ingelheim offers a non-assert declaration to all WHO pre-qualified manufacturers in least developed countries, low-income countries and all countries in Africa, stating that it will not enforce its nevirapine patent rights in these countries. To date, eleven generic producers benefit from the non-assert declaration.

- Bristol-Myers Squibb has a policy of not enforcing its patents for HIV products in SSA and has immunity-from-suit agreements with eleven African generic companies for stavudine and didanosine and with three for atazanavir. In February 2006, it concluded technology transfer agreements with generic companies, Aspen PharmaCare (South Africa) and Emcure Pharmaceuticals (India), for its newest antiretroviral, atazanavir.

- Gilead has partnered with Aspen Pharmacare, South Africa to manufacture and distribute branded and generic versions of Viread® and Truvada® in Africa. Gilead has entered into non-exclusive licensing agreements with 13 Indian generic companies, allowing them to distribute generic versions of tenofovir and tenofovir-based regimens in 95 developing countries, including India, South Africa and Thailand. The agreements include technology transfer. The generic companies are free to establish their own pricing for their products, as Gilead believes this will ensure competitive pricing and the broadest access possible for patients. Gilead receives a 5% royalty on finished product sales. Most recently Gilead announced new licensing terms with four India-based drug manufacturers for three drugs which are currently in late-stage clinical development. In addition, Gilead became the first pharmaceutical company to enter a licensing agreement with the Medicines Patent Pool Foundation.

- ViiV Healthcare committed to making its entire portfolio of ARV products available royalty-free to generic manufacturers as long as they are sold to least developed countries, low-income countries or countries in SSA in July 2010. In total, eleven royalty-free voluntary licence agreements have been extended to generic manufacturers that allow for ViiV Healthcare's ARVs to be generically manufactured and sold to all of sub-Saharan Africa.

- Merck & Co. has granted royalty-free licences of its ARV efavirenz to five generic manufacturers, of which four are currently on the market.

- Roche has committed not to file any new patents or enforce existing patents for any of its medicines in the UN-defined Least Developed Countries. Nor will it enforce existing patents for its antiretrovirals in sub-Saharan Africa. In 2006, Roche committed to an 'AIDS Technology Transfer Initiative'. Thirteen agreements have now been signed with entities from eligible countries and expressions of interest have been received from 41 more in 17 eligible countries.

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**71** "Developing World Health Partnerships Directory 2010". IFPMA (2010)
"Technology transfer: a collaborative approach to improve global health" IFPMA (2011)
**72** http://utw.msfaccess.org/drugs/

### 3.1.5 Compulsory licensing and other TRIPS flexibilities

Non-enforcement of patent rights in least-developed countries and voluntary licences in a number of developing countries have allowed access to generic versions of patented ARV drugs at competitive prices. However, middle-income countries have been generally excluded from these measures.

In a limited number of cases, national governments have chosen to respond by issuing compulsory licences allowing local generic companies to produce generic versions of patented ARV drugs. The TRIPS agreement recognises the right to issue compulsory licences under certain conditions. Two of the main such conditions are that, as a general rule, an effort must first have been made to obtain a voluntary licence on reasonable commercial terms and conditions and that the remuneration paid to the right holder shall be adequate in the circumstances of each case, taking into account the economic value of the licence.[73] Brazil and Thailand are among the few countries that have used compulsory licensing, whose use in practice remains very limited.

While there have been few cases of compulsory licensing, the threat of issuing a compulsory licence may have been useful for national governments in the price negotiations with pharmaceutical companies. It has been suggested that the threat of compulsory licensing has been successfully used in a number of cases to obtain significant discounts from branded manufacturers.[74]

The Doha Declaration includes a waiver of the TRIPS Agreement to allow the issuance of compulsory licences in countries where patents are valid to be exported to countries that lack production capacity, the so-called Paragraph 6 provision. Interestingly, Rwanda has been the only country to import generics using Paragraph 6 of the Doha declaration.[75]

The TRIPS Agreement also recognises that the protection of intellectual property and competition policy need to work harmoniously. The Agreement recognises the right of to take measures, consistent with its provisions, against anti-competitive practices and provides more flexible conditions for the grant of compulsory licences where a practice has been determined after due process of law to be anti-competitive.[76] South Africa provides an example of a country where these provisions have been used.[77]

### 3.1.6 Development of purchasing mechanisms

In addition to providing funds to purchase ARVs, one of the most significant roles of multilateral agencies such as PEPFAR and UNITAID is to participate in procurement efforts. Pooled procurement allows organisations to aggregate purchases that use funds from multiple donors or that would be made by local governments. PEPFAR was the first large-scale purchaser to implement this strategy.

The Global Fund initially chose a different approach, allowing the national participant to determine the procurement process. This changed in May 2009 with the introduction of GFATM's Voluntary Pooled Procurement (VPP) pro-

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**73** http://www.wto.org/english/tratop_e/trips_e/pharma_ato186_e.htm
**74** Beall and Kuhn (2010), "Trends in International Compulsory Licensing for Pharmaceutical", Mimeo.
**75** "Using TRIPS flexibilities to improve access to HIV treatment", UNAIDS 2010
**76** http://www.wto.org/english/tratop_e/trips_e/pharma_ato186_e.htm
**77** "Using TRIPS flexibilities to improve access to HIV treatment", UNAIDS 2010

gramme. VPP encourages countries to pool ARV volumes through third-party procurement.[78] The objective of this is to:[79]

- Leverage the Global Fund's position to influence market dynamics in order to assist Principal Recipients to obtain better prices for quality assured health products in a sustainable manner; and
- Address some of the problems faced by Principal Recipients when procuring health products, such as long procurement processes and stock-outs caused by procurement delays.

The advantages of aggregating purchasing mechanisms are relatively obvious:

- Centralising procurement means specialist agencies can be used (for example, Supply Chain Management System is used in pooled procurement for CHAI, PEPFAR and UNITAID). This allows specialists to be involved in the design of the procurement process and additional information to be taken into account;
- It could reduce transaction costs through exploiting economies of scale in the administration functions for example; and
- It could offer a solution to the problems created by corruption.

However, as set out in Waning (2010), these theoretical benefits may not occur in practice. Pooling requires harmonisation of registration, IP, ARV selection and demand forecasting. It may involve organisation with higher operating costs than those in the local markets themselves. Finally, it prevents the development of procurement skills in the local markets, with the implication that they are dependent on the multilateral organisation that might not continue indefinitely.

Finally, there is a concern that too much aggregation of purchases may lead to problems in the longer term. If procurement leads to a contract going to a small number of providers, this might ultimately reduce the competition and lead to a higher price than might otherwise occur.

The impact of centralised procurement has been significant. PEPFAR has been associated to changing the market structure for first-line FDCs.[80] The purchasing process usually consists of using a tender to choose one or two providers.[81] Figure 27 shows the relevance of centralised purchasing in the ARV market. PEPFAR and UNITAID account for half of the market value of abacavir and three quarters of emtricitabine and tenofovir. Together with the Global Fund, they are reported to account for above 85% of market value for these three drugs.[82]

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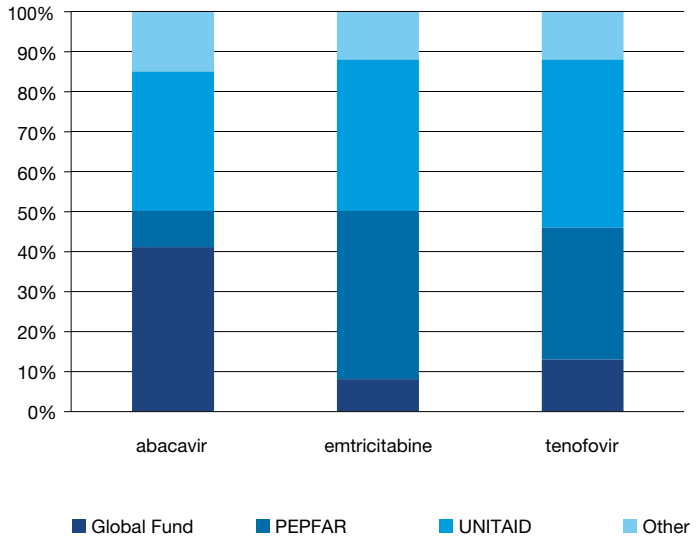
**78** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**79** http://www.jsi.com/JSIInternetProjects/InternetProjectFactSheet.cfm?dblProjDescID=6241
**80** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**81** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**82** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).

Figure 27: *Market share by buyer for abacavir, emtricitabine and tenofovir in 2008*

SOURCE: WANING ET AL (2010)




In terms of positive impact, there is some evidence from the results of this:[83]

- The Global Fund says that its Voluntary Pooled Procurement (VPP) programme has resulted in increased pooling of demand, and that has contributed to price stabilisation and market sustainability for the medicines that it procures.

- The Global Fund states that to this point in time, 42 countries have used 83 grants over the course of their participation in the VPP, far exceeding expectations. A total of $384 million in orders were confirmed by September 2010, 91% of which were for core products: long-lasting insecticide treated nets (LLINs) (78%), antiretrovirals (ARVs) (10%) and artemisinin-based combination therapies (ACTs) (3%).

- Master supply agreements were signed with manufacturers of most ARVs and ACTs. Between June 2009 and September 2010, an average decrease of 14% in the price ceilings for both ARVs and ACTs was achieved.

- Average time from the order for ARVs being placed to delivery was 6-8 months. The Global Fund said that an earlier analysis of procurement processes at the national level showed an average of 5-18 months for delivery.

However, they also identify challenges that remain as a result of the difficulty in aggregating demand effectively (due to various country- and grant-specific factors).

The impact of the other procurement programmes has been even more dramatic. The cost per person of ART in PEPFAR programmes decreased. Costs reduced by 47% from 2004 to 2006 in South Africa, and by 45% from 2003 to 2006 in Zambia. In five countries (Botswana, Ethiopia, Nigeria, Uganda and Viet-

**83** "Report of the Market Dynamics and Commodities Ad-Hoc Committee," December 2010

nam), median per-patient costs at 24-29 months after programme initiation were reduced by 37% from rates noted in the first 5 months. Another example is the programme implemented by Medecins Sans Frontieres in Malawi at US$237 per patient-year, with antiretroviral drugs forming two-thirds of the total cost. This figure is much lower than in other programmes providing ART to fewer patients in the country.[84]

The impact on the number of market structure is less clear. It is claimed that the establishment of large-scale purchasers such as PEPFAR, UNITAID and the Voluntary Pooled Procurement programme of the GFATM, which relieves individual countries of their procurement responsibilities, is rapidly consolidating the number of buyers in the market.[85]

However, it has also been observed that the market dynamics of FDC versions of ARVs are indicative of improved market efficiency over the past several years, at least using typical measures of competition.

- First, there has been a large increase in the number of manufacturers.
- In addition, the number of purchasers and total volume purchased increased.
- A reduction in the market power of suppliers has likely contributed to the reduction in price, while at the same time the increases in demand have attracted new entry by generics producers.[86]

Finally, it is important to take into account the interaction between quality assurance and procurement issues. Some of the procurement systems, such as PEPFAR only purchase from suppliers who have pre-qualified through WHO. Initiatives such as the WHO Prequalification Programme (WHO Prequal) and the Food and Drug Administration (FDA) are meant to ensure that ARVs procured with donor funds meet international quality standards, but they may also influence the rate and extent of ARV dispersion across low- and middle-income countries. There is a concern that mechanisms to assure the quality standards of generic products may have limited the number of generic producers. Quality-assured generic FDC ARVs used in newer regimens are appearing at a slower rate than that observed with older regimens.[87] Although the role of WHO and the FDA has a positive impact in guaranteeing certain standards of quality and correcting information asymmetries between buyers and suppliers, delays in quality certification can also create delays in country uptake of products, as demonstrated by a three-year wait to use PEPFAR funds for the most commonly-used fixed-dose combination (lamivudine+nevirapine+stavudine).[88]

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**84** Schwartlaender et al. (2011), "Towards an improved investment approach for an effective response to HIV/AIDS", Lancet 377: 2031-41.
**85** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**86** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**87** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).
**88** Waning et al. (2010), "Intervening in global markets to improve access to HIV/AIDS treatment: an analysis of international policies and the dynamics of global antiretroviral medicines markets", Globalization and Health, 6(9).

### 3.1.7 Capacity building

Patients' access to ART is not only dependent on the supply of the ARV drugs themselves, but also on the ability of local healthcare systems to provide these drugs to the patients on the ground-level. Structural weaknesses in the healthcare infrastructure in many developing countries could constitute a bottle-neck in the provision of ART. These weaknesses can include a lack of organisational capacity, insufficient testing and treatment facilities in close proximity to HIV patients, and inadequate training of healthcare professionals in the management of HIV/AIDS patients. Logistical limitations often hamper the ability of providers to reach certain population groups, such as rural populations and those at earlier stages of HIV infection.[89] In many places, HIV services, services to advance sexual and reproductive rights, and other health services are not integrated and vital opportunities to reach women and young people are missed.[90] Infrastructural deficits are particularly relevant where the HIV/AIDS epidemic affects the general population, given the importance of provider-initiated testing and care in those settings.

The management of HIV/AIDS epidemics requires the permanent and integrated provision of healthcare services to vulnerable populations and to people living with HIV. Diagnosis, testing, provision of ARV drugs, patient surveillance and support, and programmes to educate and reduce stigma are all components that contribute to the expansion of access to ART and ultimately, therapeutic success in treatment. Structural weaknesses of healthcare systems in developing countries often mean that the provision of all these services is suboptimal, which impedes the expansion of access to ART for patients.

Contributing to the strength of local health systems has been one of the priorities of international donors of aid for HIV/AIDS. GAVI Alliance, the Global Fund and the World Bank are the largest providers of support for broad health system development. In collaboration with WHO, they have jointly developed the Health Systems Funding Platform to coordinate their efforts. The overarching goal is to help building stronger health systems that are more able to deliver adequate healthcare services. Although the platform is intended to facilitate coordination in funding health system improvements, each of the three partners continues to fund interventions separately.

The Global fund, for instance, committed around $1.5 billion between 2005 and 2008 in grants to strengthen health systems. The main beneficiaries of these grants were Ethiopia, Nigeria, Philippines, Malawi, Rwanda and Zimbabwe, among others. The largest commitments were for human resources together with training, followed by infrastructure and equipment.

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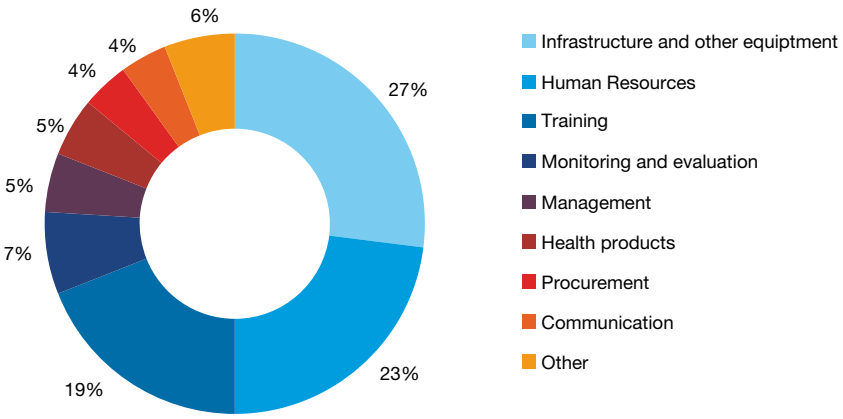
**89** Lima et al. (2008), "Expanded Access to Highly Active Antiretroviral Therapy: A Potentially Powerful Strategy to Curb the Growth of the HIV Epidemic", Journal of Infectious Diseases, 198: 59-67.
**90** Girard et al. (2010), "Universal Access in the Fight Against HIV/AIDS", Science, 329: 147-149.

Figure 28: *Breakdown of approved funding for health systems strengthening in Global Funds' Round 8*

SOURCE: GLOBAL FUND [91]




The fact that most of the main recipients of funding have been countries in SSA is unsurprising. The biggest challenges for the response to HIV lie in countries with generalised HIV epidemics, where HIV increases the workload of the health sector while undermining the capacity of its workforce.

### 3.1.8 Programmes to overcome stigma

The lack of education programmes and the dearth of information available to both the general population in countries with generalised epidemics and the vulnerable populations where there are concentrated epidemics is also a significant barrier. Lack of adequate information is a barrier to prevention programmes that seek to reduce HIV transmission through the promotion of safe practices. It also reduces the number of patients who might otherwise seek counselling and care. Awareness of the availability of treatment has shown to be a significant factor for patients initiating ART. Often regarded as a derivative of a lack of HIV/AIDS education, the existence of social stigma has also been identified as an important barrier for access to care. The stigma associated with HIV/AIDS, especially where the epidemic is concentrated in certain vulnerable populations, leads HIV-infected people to not seek treatment in order to avoid the risk of social exclusion.

Research shows that interventions to reduce stigma are effective. However, complete elimination of stigma is likely to be more an aspirational than a realistic goal. Intervention strategies that have proved effective at reducing stigma include information campaigns, counselling, coping skills acquisition and community work. Studies with a control group show that these interventions are effective at changing attitudes and behaviours. Most experiences from low- and middle-income countries come from community-based interventions, in contrast with the rather individual approach in high-income countries. [92]

**91** http://www.theglobalfund.org/en/performance/effectiveness/hss/target/
**92** Brown et al. (2001), "Interventions to reduce HIV/AIDS stigma: what have we learned", Horizons Program, Tulane University.

There is less evidence on the long-term effectiveness of interventions to reduce stigma. Long-term effects cannot be taken for granted given the inertia that often characterises collective attitudes. Another issue that requires further attention is layered stigma, which occurs when HIV-related stigma appears in conjunction with other social stigmas, such as those associated with commercial sex work and injection drug use.[93]

### 3.1.9 Partnerships

In this chapter so far we have set out the activities undertaken to improve access to ARVs over the last ten years and the involvement by multi-national organisations, national governments, non-governmental organisations and the private sector including the pharmaceutical industry. In reality, one of the most important elements of responding to the AIDS crisis has been partnership.

**Public-private partnerships**

Public-private partnerships (PPP) have been a critical part of HIV/AIDS responses over the last ten years. PPPs are defined as being voluntary and collaborative relationships that bringing together state and non-state actors to undertake specific functions in health governance.[94] These are commonly broken into two groups:

- The first type, partnerships operated by International Agencies, invites participation of private sector actors.
- The second grouping includes partnerships that are independently structured non-profit entities with private governance, operations and financing.

The number and diversity of partnerships between local government, NGOs and technical support is vast in the area of HIV/AIDS. The Global Fund itself is a public-private partnership established in 2002 to mobilise and intensify the international response to three global epidemics and thereby help achieve the Millennium Development Goals.[95]

Partnerships have been important from the beginning of the decade. The Accelerated Access Initiative (AAI)[96] established at the international level in May 2000 to increase access to HIV/AIDS treatment in developing nations and high burden middle-income nations. It consists of a partnership between the UN and seven pharmaceutical companies: Abbott Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, F. Hoffmann La-Roche, Gilead Sciences and Merck & Co.

**ART as a component of an integrated response to HIV/AIDS**

The importance of partnership is further supported by the recognition that ART

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**93** ICRW (2006), "HIV/AIDS stigma. Finding solutions to strengthen HIV/AIDS programs"
**94** Brown (2007), "Global Public-Private Partnerships for Pharmaceuticals: Operational and Normative Features, Challenges, and Prospects", Mimeo.
**95** The Global Fund defines its partnership as the core to its success through relying on the financial pledges of donors, the technical guidance of — and collaboration with — multilateral partners, and particularly the management and implementation of programmes by in-country partners including governments, civil society organisations and the private sector.
**96** The Accelerated Access Initiative was announced in May 2000 and consists of a partnership between five UN organisations and six pharmaceutical companies. The AAI works with governments, international organisations and the private sector to negotiate differential drug prices

is only part of the solution and needs to be integrated into the overall response to the epidemic. This has recently been emphasised in the proposals by Schwartlaender et al. (2011).They propose a strategic investment framework that is intended to support better management of national and international HIV/AIDS responses than exists with the present system. They argue there are major efficiency gains through community mobilisation, synergies between programme elements, and benefits of the extension of antiretroviral therapy for prevention of HIV transmission.[97] They argue: *"Unsystematic prioritisation and investment were allowed to persist as interests and stakeholders competed for a proportion of available funding for HIV/AIDS, spreading resources thinly between many objectives."*

This brings together: provider-initiated HIV testing or other health-facility HIV testing services (use of voluntary counselling, testing centres or other testing approaches are counted as critical enablers in this framework) and support for treatment adherence, including family and community approaches, which can improve access to HIV/AIDS services, drug-adherence, morbidity and mortality outcomes, and antiretroviral therapy component.

**The link between prevention, treatment and co-morbidities**

As set out in Chapter 2, new evidence suggests treatment with ARVs also supports the prevention programme, reducing the number of people ultimately needing treatment. At a simpler level, prevention and treatment programmes are clearly linked — to the extent that prevention succeeds, there is smaller population requiring access to ARV and the resources required to treat this population are more manageable.

This becomes even more challenging over time. Schwartlaender et al. (2011) discuss how the rapid expansion in the number of people receiving antiretroviral therapy means health systems must continue to provide preventive interventions and acute life-saving care for those with advanced AIDS while also providing long-term services to growing cohorts of more stable patients receiving antiretroviral therapy who will develop non-communicable diseases and comorbidities as a result of longevity, long-term effects of HIV and effects of protracted antiretroviral therapy.[98]

The importance of focusing on the whole package is emphasised as service delivery costs account for almost two-thirds of the total cost of antiretroviral therapy.[99]

## 3.2 SUMMARY

Each country has developed a different mix of interventions, giving stronger emphasis to some of them over the others according to their institutional and economic framework, as well as to the characteristics of their HIV/AIDS epidemic. Some intervention-mixes may have proved more effective than others in specific settings and the results attained by different countries over the last decade may provide valuable lessons about the relative efficacy of these sets of interventions. We review these in the next chapter.

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**97** Schwartlaender et al. (2011), "Towards an improved investment approach for an effective response to HIV/AIDS", Lancet 377: 2031-41.
**98** Schwartlaender et al. (2011), "Towards an improved investment approach for an effective response to HIV/AIDS", Lancet 377: 2031-41.
**99** Schwartlaender et al. (2011), "Towards an improved investment approach for an effective response to HIV/AIDS", Lancet 377: 2031-41.

# 4

# LESSONS FROM THE CASE STUDIES

To try to understand the contribution that different policy interventions, described in the previous chapter, have made to the improvement in access to ART reported in Chapter 2, we have reviewed the experience of seven countries. In this chapter, we first summarise the experience of each of these markets, and then we draw on these experiences to examine the importance of the different interventions.

## 4.1 EXPERIENCE OF THE SEVEN CASE STUDIES

Although there is wide variation in our case study countries in geography, wealth and the nature of each epidemic, in all of the case studies examined there has been significant progress in expanding access to ART over the last decade. This is summarised in Table 6.

As set out in the previous chapters, it is also important to recognise that different countries faced significantly different challenges depending on each country's income (and therefore ability to fund programmes domestically without access to international assistance) and the nature of the epidemic. However, for each case study we try to examine how the improvement in access is related to the HIV/AIDS programmes, the wider investment in health care infrastructure and the method of purchasing ART.

Table 6: *Overview of case studies*

SOURCE: CRA ANALYSIS

| | | Botswana | Brazil | India | Mexico | Rwanda | South Africa | Thailand |
|---|---|---|---|---|---|---|---|---|
| Category | Region | Africa | Latin America | Asia | Latin America | Africa | Africa | Asia |
| | Income group as at 2000* | Upper middle income | Upper middle income | Lower middle income | Upper middle income | Low income | Upper middle income | Lower middle income*** |
| | Type of epidemic | Generalised | Concentrated | Concentrated | Concentrated | Generalised | Generalised | Concentrated |
| Political Will | Year of HIV universal service | 1999 | 1996 | 2004 | 2003 | 2002 | 2004 | 2000 |
| Spending | Share of HIV spending on treatment (including infrastructure, staff, drugs, etc.) | 48.6% on treatment | 83.9% on treatment | 37.2% on treatment | 74.8% on treatment | 40.3% on treatment | Not available | 76% on treatment |
| | Involvement of the international community | 67.3% domestic funded, ACHAP a significant component | 99% domestic funded | 16.5% domestically, Global Fund a significant funder | 99.4% domestic funded | 8.2% public funding, with the rest through Global Fund and bilateral funding | 72.7% public funding, with the rest through bilateral funding | 90% public funding, with the rest through Global Fund |
| IP | Local generic industry | No | Yes | Yes | No | No | Yes | Yes |
| | Government own manufacturer | No | Yes | No | No | No | No (under debate) | Yes |
| | Use of compulsory licensing | No | Yes | No | No | No | No | Yes |
| | Use of Paragraph 6 | No | No | No | No | Once | No | No |
| Access | ART coverage 2004** | 46% | 83% | 5% | 46% | 13% | 5% | 27% |
| | ART coverage 2009** | 95% | 80% | 41% | 71% | 95% | 56% | 76% |

NOTES:
* World Bank categorisation,
** ART coverage according to 2006 WHO guidelines,
*** changed in 2011

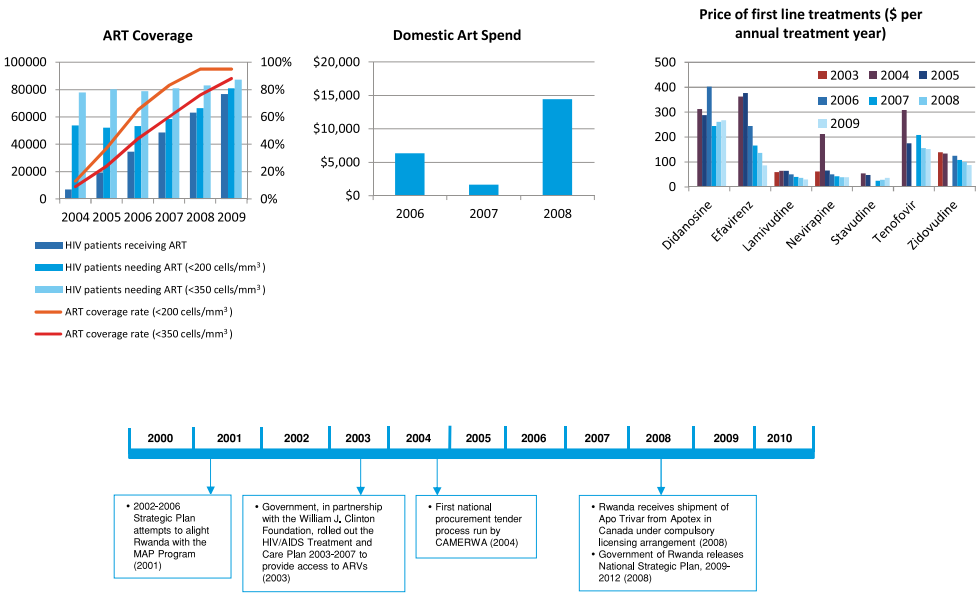
## 4.2 LOW-INCOME COUNTRIES

### 4.2.1 Rwanda

Rwanda is the only low-income country in our case studies. It faced a generalised epidemic, with HIV/AIDS affecting all segments of the population in Rwanda. The first HIV/AIDS cases were documented in 1983, making Rwanda one of the first African countries to recognise the virus.[100]

Figure 29: *Overview of Rwanda*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




Early efforts to curb the epidemic focused on prevention and education, and as of 2003, there were only seven sites that provided ARV treatment to the public.[101] Since then, there have been several initiatives to increase access. Most notably, the government, in partnership with the Clinton Foundation, initiated the HIV/AIDS Treatment and Care Plan 2003-2007 in 2003. This programme was created to "develop and deliver standardised, nationally available comprehensive treatment and care services to Rwandans living with HIV/AIDS," and it was the first national initiative that focused principally on providing ART to the public.[102]

While the health system in Rwanda is generally considered quite poor, funding from external organisations and their focus on HIV/AIDS treatment has dramatically improved treatment for HIV/AIDS, even as challenges facing other health conditions remain significant. In addition to the expansion of the treatment programme, there has been a significant increase in the amount of HIV testing, both as a result of expanding the number of facilities offering the tests, and the creation of programmes that educate people on the importance of testing. The

**100** Kayirangwa, Hanson, Munyakazi, et al, "Current Trends in Rwanda's HIV/AIDS Epidemic," Sex Transm Infect, 2006.
**101** "HIV/AIDS Treatment and Care Plan 2003-2007," Republic of Rwanda, June 13, 2003.
**102** "HIV/AIDS Treatment and Care Plan 2003-2007," Republic of Rwanda, June 13, 2003.

number of health clinics offering voluntary counselling and testing has increased dramatically, from 44 in 2003 to 395 in 2009.[103] One of the things that have been integral to the expansion of HIV/AIDS-related programmes has been the National AIDS Spending Assessment programme, which tracks the flow of resources in the response against HIV/AIDS. Faith-based organisations (FBOs) have also played a very active role, and are responsible for administering about 40% of the health network in Rwanda, which includes testing and ART facilities.[104]

As one of the poorest countries in the world, Rwanda has depended heavily on international support to combat HIV/AIDS. Public funding for HIV/AIDS sourced from Rwanda was only $4.3 million in 2006, after which it increased to $6.1 million in 2008, which was 5.5% of total funding in that year. International funding accounted for $80.4 million of HIV/AIDS spending in 2006, and while this declined in 2007, it increased to $104.7 million in 2008, or 94.5% of total funding.[105] International sources have therefore accounted for the vast majority of funding for HIV/AIDS programmes.

In an effort to procure cheaper ARVs through exploiting economies of scale, the government initially relied on group purchasing from the Clinton Foundation to supply its ARV programme. Then, in October 2004, the Rwandan Ministry of Health issued a Ministerial Order that required all ARVs to be procured by the Centrale d'Achats des Médicaments Essentiels Consommables et Equipements Medicaux du Rwanda (CAMERWA), a national agency for pharmaceutical procurement. CAMERWA requires any providers to prescribe ARVs according to the guidelines of WHO, which means that WHO-approved generics are used as first-line treatment, then brand-name ARVs are used if patients require second-line ARVs.[106]

Rwanda is the only country so far to have taken advantage of the TRIPS flexibilities associated to licensing generic manufacturers in other countries. In 2007, Rwanda notified the WTO that it was planning to take advantage of the compulsory licensing provisions set out in the amendment to Article 31, and in Canada's Access to Medicines (CAMR) by importing generic Apo TriAvir from Canada.[107] Before starting the CAMR process, Apotex needed to amend the list of pharmaceutical products that qualified for generic manufacturing and receive an expression of interest from a destination country. The review of the application was completed in six months and in August 2006 Apotex received manufacturing approval.[108] During the following year, Apotex sought a recipient country interested in Apotex's product and in July 2007 Rwanda expressed interest. Following CAMR requirements, Apotex negotiated with the three brand manufacturers and within three weeks all brand manufacturers issued voluntary licences or agreed to the issuance of compulsory licences by Canadian authorities. Apotex was granted all necessary licences by September 19th, 2007, but the supply contract was not awarded by the Rwandan government until eight months later.[109] Rwanda gave Apotex final tender approval in May 2008, and the first shipment was received in

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**103** "The AIDS Response and the Millennium Development Goals: Rwanda Case Study," UNAIDS, 2010."
**104** "The Africa Multi-Country AIDS Program: 2000-2006," World Bank, 2007.
**105** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**106** "Rwanda: Pooled Procurement and Capacity-Building Help to Scale up Treatment," PEPFAR, April 2007.
**107** "A One-Time-Only Combination: Emergency Medicine Exports Under Canada's Access to Medicines Regime," Health and Human Rights, Volume 12, 2010.
**108** Tsai, George, "Canada's Access to Medicines Regime: Lessons for Compulsory Licensing Schemes under the WTO Doha Declaration," Virginia Journal of International Law, 2009.
**109** WTO TRIPS Council, Minutes of meeting held on 2 March 2010. Document IP/C/M/62, paragraphs 187-195.

September 23, 2008.[110] The overall process proved lengthy and it turned out to be particularly difficult for Apotex to find recipient countries interested in using Paragraph 6 provisions. In fact, this is the only use of the CAMR legislation since its adoption. This has therefore not been an important factor in the increase in access to ART.

There is no disputing that Rwanda has successfully responded to the HIV epidemic. It now has one of the highest rates of ART coverage of any country in Africa, almost 90% by the newest WHO guidelines.[111] This has been possible due to early recognition of the epidemic, which was followed by strong political leadership, and international support for healthcare infrastructure, purchasing and logistics. It is important to recognise that while the coverage rates are quite high, the number of people receiving ART is relatively small (80,000). While this is a significant improvement from the 7,000 people who were receiving treatment in 2004, one of the reasons that the ART programme was able to ramp up so quickly was the relatively small total population, which would not be the case in a larger country such as South Africa.

## 4.3 LOWER MIDDLE-INCOME COUNTRIES

### 4.3.1 India

India has one of the largest populations affected by HIV in the world, third only to South Africa and Nigeria.[112] As a densely populated nation with a high degree of poverty, India is very vulnerable to epidemics and HIV/AIDS has grown rapidly since the first case was seen in the late 1980s.[113] In addition, to being an illuminating case study in its own right, India has played an important role in supplying generic ART coverage to other developing markets.

Since Cipla released its revolutionary FDC drug in 2001, Indian generic firms have become significant manufacturers of ARVs, largely because the lack of patent protection for these medicines eliminated the need for licensing agreements until 2005.[114] Following the lead of Cipla, numerous other generic firms also entered into the production of ARVs, and by 2007 there were 14 Indian firms that were active in producing generic ARVs, and almost every first-line ARV is now produced generically.[115] India is now the largest supplier of generic ARVs to low- and middle-income countries. It supplies an estimated 80%of donor-funded ARVs to these countries.[116] It is clear that the expansion of generic manufacturing in India has contributed to the implementation of universal access to ARVs in a number of other countries. However, at the same time, India continues to face challenges in providing ARVs to its native population.

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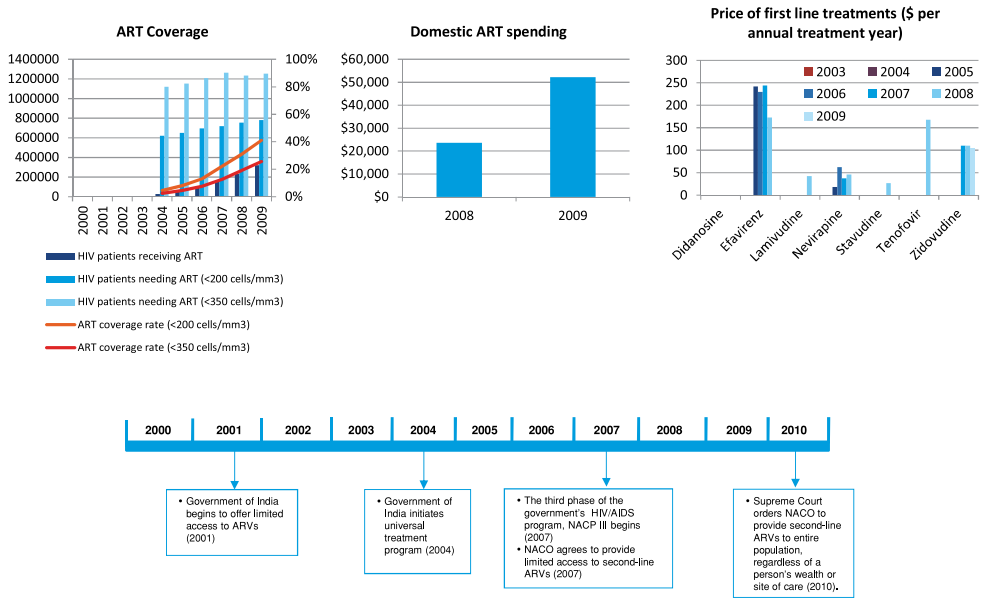
**110** Tsai, George, "Canada's Access to Medicines Regime: Lessons for Compulsory Licensing Schemes under the WTO Doha Declaration," Virginia Journal of International Law, 2009.
**111** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**112** "Country Progress Report — India," UNGASS, March 31, 2010.
**113** "Overview of HIV and AIDS in India," AVERT, viewed on 18/7/2011, http://www.avert.org/aidsindia.htm.
**114** George, Julie, "Intellectual Property and Access to Medicines: Developments and Civil Society Initiatives in India," Lawyers Collective HIV/AIDS Unit, 2009.
**115** Dhar, Biswajit and Gopakumar, KM, "Effect of Product Patents on the Indian Pharmaceutical Industry," 2007.
**116** "AIDS, Drug Prices and Generic Drugs," AVERT, viewed on July 29, 2011, http://www.avert.org/generic.htm.

Figure 30: *Overview of India*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




Although India has had an HIV/AIDS programme since the 1980s, the implementation of a universal treatment programme for HIV/AIDS did not occur until 2004. In its initial response in the early 1990s, the government created the National AIDS Control Organisation (NACO) and initiated a strategic plan, known as the National AIDS Control Programme (NACP) that focused on preventative strategies.[117] In 1999, the NACP entered its second phase (NACP II), which aimed to reduce the spread of HIV through behavioural change.[118] At this time, ARVs were available through the private sector but the majority of the infected population was unable to afford the treatments.[119] It wasn't until 2001 that the government began to provide ARVs, and until 2004, they were only provided for preventative purposes.[120] Even though large-scale price reductions for first-line ARVs occurred worldwide in 2001, the government deferred the provision of ART, specifically citing "prohibitive costs". [121]

In April 2004, the government of India finally initiated a universal public ARV programme, through which first-line ARVs were provided to the infected population at eight health centres in six of the highest prevalence states and in the capital city of Delhi. Scaling up of the programme was slow, but by 2008, there were 137 centres in 31 states that provided ART.[122] The number of available first-line drugs was also expanded as more generics became available and costs

**117** "Overview of HIV and AIDS in India," AVERT, viewed on 18/7/2011, http://www.avert.org/aidsindia.htm.
**118** "Spotlight: National AIDS Control Programme," Government of India, viewed on July 28, 2011, http://india.gov.in/spotlight/spotlight_archive.php?id=34.
**119** George, Julie, "Intellectual Property and Access to Medicines: Developments and Civil Society Initiatives in India," Lawyers Collective HIV/AIDS Unit, 2009.
**120** George, Julie, "Intellectual Property and Access to Medicines: Developments and Civil Society Initiatives in India," Lawyers Collective HIV/AIDS Unit, 2009.
**121** "Our Health Our Right: The Roles and Experiences of PLHIV Networks in Securing Access to Generic ARV Medicines in Asia," Asia Pacific Network of People Living With HIV/AIDS, 2008.
**122** "Country Progress Report — India," UNGASS, March 31, 2010.

decreased.[123] The provision of second-line treatments did not occur from the outset. While NACO agreed to initiate a programme providing limited second-line treatment on December 1, 2007, it wasn't until December 2010 that the Supreme Court of India ordered NACO to provide second line treatment to the entire population, regardless of a person's wealth or the site of their prior first-line treatment.[124]

The third phase of the NACP (NACP III) commenced in 2007 and runs until 2012.[125] NACP III continues to allocate more resources for prevention efforts than for treatment. It has a budget of approximately $2.6 billion, of which two-thirds is budgeted for prevention efforts and only one-sixth is for treatment.[126] The funding for this programme has been committed by the government, international organisations such as the World Bank, and the Bill and Melinda Gates Foundation.[127] NACP III has aimed to open 250 ART centres by the end of 2011.[128]
Funding for HIV/AIDS initiatives has been largely from the international community. As a percentage of the total funding for HIV/AIDS responses, public funding accounted for only 16.5% in 2009. The Global Fund was the largest single supporter, accounting for 41.1% of funding in 2009. Bilaterals and other multilaterals account for 41.7%, and the UN directly funds 0.7%.[129]

NACO negotiates drug prices with Indian generic manufacturers for first-line ARVs through a public tender process.[130] In the past, NACO has been very successful at attaining the lowest prices for first-line ARVs, although this is partly due to the lack of a pre-qualification requirement, which widens the supplier pool more than might be the case in other countries.[131]

Along with providing ART, NACO has also been responsible for the creation of hundreds of integrated counselling and testing centres (ICTCs). ICTCs have also been created by NGOs and other external organisations.[132] While there were just 62 of these centres in 1997, by the end of 2009, there were 5,135 centres with integrated counselling and testing in India.[133] Between 2006 and 2009, there were 9.4 million people tested for HIV.[134]

India has improved access to ARTs over the last decade, but there remain significant challenges. According to 2006 WHO Guidelines, 780,668 people required ART in 2009, which indicates a coverage rate of 41%. While there is improvement, it is clear that irrespective of which guidelines are used, ART coverage remains limited in India. There are also large degrees of variability in access to care between states (and sometimes within states). While low generic prices are important for expanding access to treatment, they are not sufficient by themselves to raise ART coverage rates. The healthcare infrastructure and funding also need to be sufficient to effectively provide testing, diagnosis and treatment.

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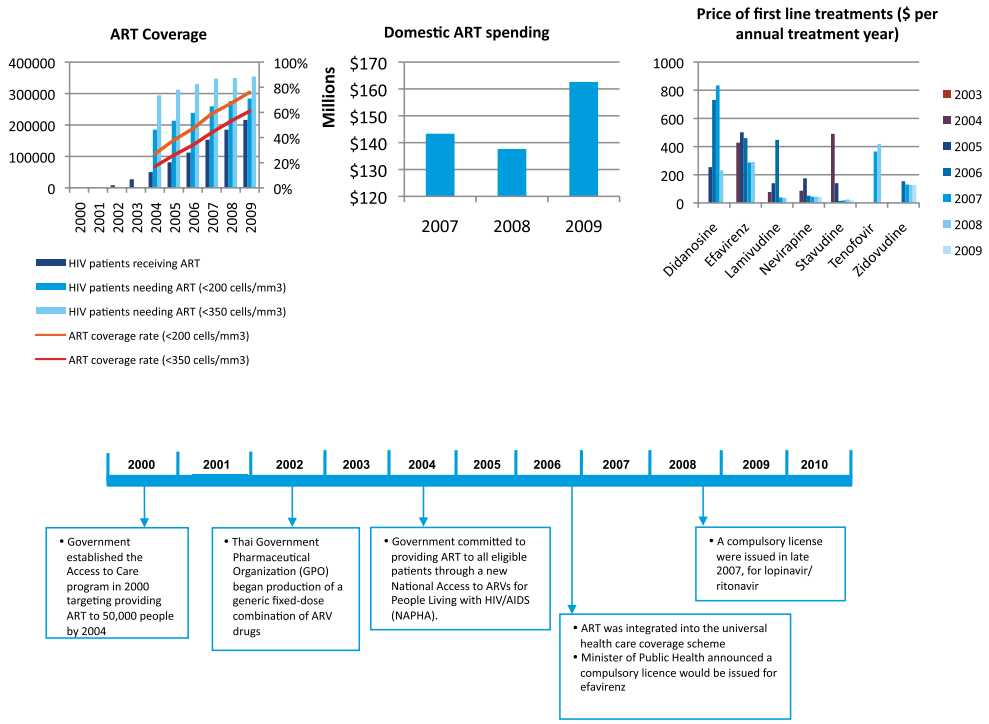
**123** Satyanarayana, Kanikaram and Srivastava, Sadhana, "Patent Pooling for Promoting Access to Antiretroviral Drugs (ARVs) — A Strategic Option for India," The Open AIDS Journal, 2010.
**124** "SC Cautions Government Over HIV Treatment," Hindustan Times, December 11, 2010.
**125** "Country Progress Report — India," UNGASS, March 31, 2010.
**126** Steinbrook, Robert, "HIV in India — The Challenges Ahead," The New England Journal of Medicine, March 22, 2007.2
**127** "India Primarily to Promote Condom Use in its HIV Prevention Programs, Health Minister Says," Henry J. Kaiser Family Foundation, September 5, 2006.
**128** "Obstacles in Accessing Treatment — Lessons from India," Panos, March 2007.
**129** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**130** "Procurement Manual for National AIDS Control Programme (NACP III)," Ministry of Health and Family Welfare, Government of India, July 28, 2007.
**131** India and Second-Line ART — Evaluating the Way Forward," Indian Network for People Living with HIV/AIDS, March 2007.
**132** "Overview of HIV and AIDS in India," AVERT, viewed on 18/7/2011, http://www.avert.org/aidsindia.htm.
**133** "Country Progress Report — India," UNGASS, March 31, 2010;" UNGASS India Report: Progress Report on the declaration of commitment on HIV/AIDS," NACO, 2005.
**134** "Country Progress Report — India," UNGASS, March 31, 2010.

## 4.3.2 Thailand

Thailand provides an example of a lower-middle income country[135] that has been able to substantially improve access to ARVs even though it has the highest levels of HIV prevalence of any country in its region.

Figure 31: *Overview of Thailand*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




Although large-scale ART programmes only started in Thailand in 2000, the Thai government had been active since the 1990s. In 1992, the Ministry of Health started supplying zidovudine monotherapy free of charge to low-income patients in public hospitals. In 1995, two dual therapies were introduced as a first-line treatment: zidovudine+didanosine and zidovudine+zalcitabine. These early initiatives, however, remained very limited and the focus of most initiatives was on prevention. By 1994, less than 5% of the people needing ART were being effectively treated.

In the late 90s, the government established the HIV Clinical Research Network with the aim of developing protocols and technical capacity to provide large-scale HIV/AIDS treatment and care (prompted by NGOs encouraging clinical trial activity within the country). In parallel, civil societies efforts also grew, with NGOs and patient groups supporting the activities of 'day care centres' for HIV/AIDS patients. The Thai government established the Access to Care programme in 2000, which had a target to provide ART to 50,000 people by 2004. The pro-

135 Thailand was re-categorised as upper middle-income countries in 2011.

gramme created the basis for cooperation between private and public hospitals and included participation from both governmental institutions and civil society. In 2002, access to treatment expanded when the Thai Government Pharmaceutical Organisation (GPO) began production of a generic fixed-dose combination of several ARV drugs, named GPO-VIR, which contained stavudine, lamivudine and nevirapine. In 2004, the Thai government committed to providing ART to all eligible patients through a new programme, known as National Access to ARVs for People Living with HIV/AIDS (NAPHA). Finally, in 2006 ART was integrated into the universal healthcare coverage scheme.[136]

Thailand has been able to fund the establishment of its large-scale ART programme largely through its own domestic resources. Domestic funding accounted for more than 90% of total HIV/AIDS spending in 2009. The contribution from external sources of funding has been limited, and comes mainly from the Global Fund.

In terms of procurement, public bodies are required to purchase through its domestic supplier, GPO. GPO manufactures a number of the ARVs it supplies, and then procures additional ARVs from other suppliers. Prices and conditions of supply are negotiated by the national government with the pharmaceutical companies. Orders for ARV drugs financed through other funding mechanisms, like the Global Fund, are placed directly by health facilities to suppliers.

In a small number of occasions, negotiations between the government and the pharmaceutical companies have failed, leading to the issuance of compulsory licences. The first example of this was for the drug efavirenz. Following failed negotiations with Merck & Co. for a lower price, the Thai Minister of Public Health announced in November 2006 that a compulsory licence would be issued for efavirenz, and supply started in February 2007. A second compulsory licence was issued under similar circumstances in late 2007 for lopinavir/ritonavir. While these compulsory licences were for widely used ARVs, most ARV drugs have not been affected by compulsory licensing. Moreover, evidence indicates that prices of the drugs that have been object of compulsory licensing had already decreased substantially before the issuance of the licences.[137] Rather, Thailand has usually been successful in purchasing first-line medicines at relatively low prices and the direct impact of compulsory licences does not seem to have been significant.

The number of HIV/AIDS patients receiving ART in Thailand has increased steadily over the last decade. In 2002, only 2,000 patients were treated but this has grown to more than 200,000 patients receiving ART in 2009. This level of ART coverage was slightly below 80% using the 2006 WHO guidelines, and slightly above 60% using the new 2010 guidelines. In examining this evolution, Thailand demonstrates a successful ART programme primarily funded domestically, but drawing on the expertise of external partners. Thailand's access to ARVs is often highlighted due to the use of compulsory licensing. However, the actual occurrence of this practice has been limited to only two occasions, suggesting a limited impact, and most medicines are purchased from international sources.

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**136** Chasombat et al. (2009), "National expansion of antiretroviral treatment in Thailand, 2000-2007: program scale-up and patient outcomes", Journal of Acquired Immune Deficitary Syndrome, 50(5).

**137** According to the evidence analysed by Thailand's Senate in "The CL Impact Study Subcommittee" and provided by the local trade association:

- Prices of Lopinavir+Ritonavir had decreased from 19,046 bath/bottle in 2004, to 5,939 bath/bottle in 2006. After compulsory licensing in January 2007, the price was 3,488 in April 2007.
- Prices of Efavirenz 220mg had decreased from 5,992 bath in 2000 to 1,904 in 2006. After compulsory licensing in November 2006, price was 1,289 bath, which is still the current price.

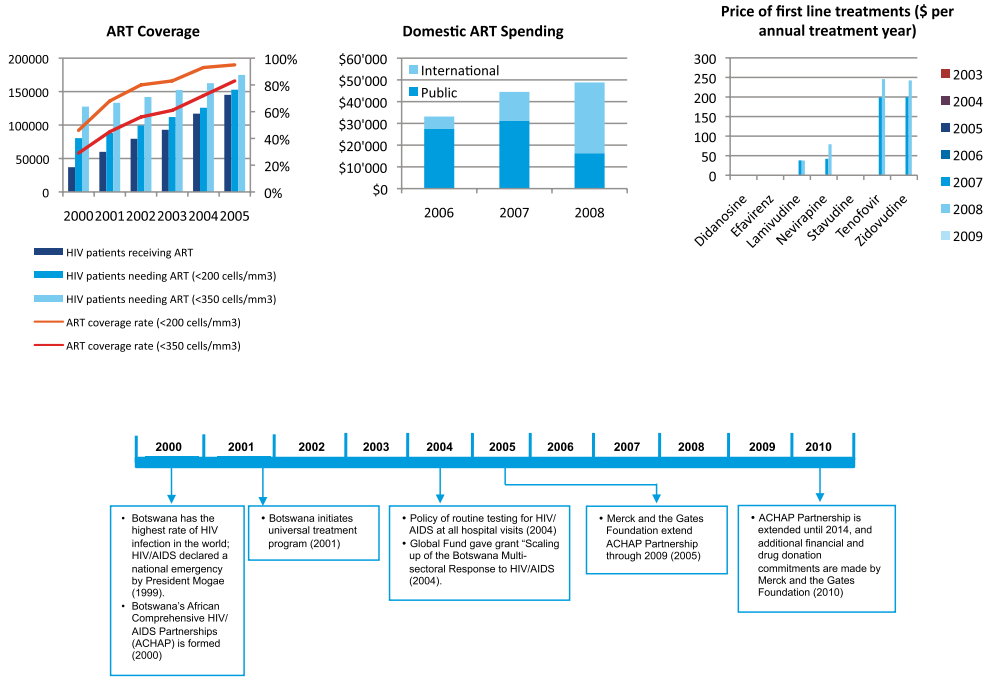
## 4.4 UPPER MIDDLE-INCOME COUNTRIES

### 4.4.1 Botswana

Botswana is an interesting case study because it is an upper middle-income country in SSA (with one of the highest GDPs per capita of any country in Africa) that faced a generalised epidemic with one of the highest rates of HIV infection in the world. While it is one of the most seriously affected countries, Botswana's ARV programme is often used as a model of success.

Figure 32: *Overview of Botswana*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




Botswana's response to HIV/AIDS started in earnest in 1999, when the President of Botswana declared the epidemic a national emergency. Shortly after, in 2001, Botswana became the first country in Africa to decide to offer ARVs universally to any of its affected citizens through the public health system.[138] This involved considerable investment, the majority of which was funded domestically. It is estimated that the government contributes 2-3% of GDP to support AIDS prevention, care and treatment, which constitutes 80-90% of the required resources for treatment.[139]

However, partnership with other stakeholders was also critical, principally through the African Comprehensive HIV/AIDS Partnerships (ACHAP), but also with PEPFAR and the Global Fund. ACHAP is a public-private partnership between the Bill & Melinda Gates Foundation, Merck & Co. / the Merck Company

**138** Rook, Franziska, "Public-Private Partnerships in the Fight Against HIV/AIDS: A Case Study of Botswana," SPNA Review: Vol. 5, 2009.
**139** "Partnership Framework for HIV/AIDS 2010-2014," PEPFAR, 2009.

Foundation and the government of Botswana that was initiated in July 2000.[140] This began with an initial $50m donation from each of the partners, the Gates Foundation and The Merck Company Foundation,[141] in addition to donations Merck antiretroviral medicines (Stocrin and Crixivan).[142] Additional drug donations have also been made by other companies.[143] In addition to donations, Botswana has also established a Central Medical Store (CMS) system, which handles all of the procurement of ARVs, including budgeting, tendering and ordering.[144] Botswana's procurement system has also been supported by PEPFAR (through SCMS), primarily receiving logistical support, but it has not used PEPFAR for pooled procurement.[145]

The progress of ACHAP illustrates the need to develop infrastructure capacity and funding of medicines in parallel. In the early part of the decade, there were not sufficient physicians, nurses or healthcare professionals, so there were situations where people were not getting treatment even though the drugs were available. Building capacity in a country requires time and expertise, but it often must happen before significant amounts of money can be used to further the efforts. This was illustrated by ACHAP, which was unable to use a substantial amount of the money it had allocated in its first several years.[146]

By the end of 2009, efforts to increase access to ARVs had been very successful: 87% of the population in need of treatment was able to receive it (140,000 people).[147] Treatment is now available in every district with 32 main sites and over 100 clinics. Beyond initiation of treatment, Botswana has been successful in maintaining treatment with treatment adherence greater than 90%.[148] The Prevention of Mother-to-Child Transmission of HIV (PMTCT) programme has also been very successful with over 90% of HIV-positive women receiving ARVs to prevent transmission of HIV to their children.[149] The successes of the ART and PMTCT programmes becomes even clearer after seeing that the number of AIDS deaths has been reduced by more than half since 2003.[150]

Botswana has demonstrated a successful model for offering universal access to ARVs. Indeed, the attention and commitment from the international community was in part to demonstrate the effectiveness of partnership programmes of this kind; ACHAP was the first public-private partnership that demonstrated the feasibility of large-scale HIV treatment through Botswana's national ARV treatment programme, Masa. However, it also showed that even with significant resources and a relatively developed healthcare infrastructure, improvements in ART coverage take time to achieve. It has also been recognised that a partnership like ACHAP could not be replicated in exactly this fashion across any country. Botswana continues to face challenges going forward, especially as it tries to fund ART access for the increasing population living with AIDS that will continue to grow as patients live longer. The need to focus on prevention has been recognised

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**140** Rook, Franziska, "Public-Private Partnerships in the Fight Against HIV/AIDS: A Case Study of Botswana," SPNA Review: Vol. 5, 2009.
**141** Both foundations have renewed their commitment, with further donations of $30m each for the period 2010-2014.
**142** Merck extended the donation programme to include its new drugs Atripla and Isentress when they were launched in 2008. In 2010, Merck committed to continue the programme of donations of all its antiretroviral drugs through 2014.
**143** "Impact of Public-Private Partnerships Addressing Access to Pharmaceuticals in Low and Middle Income Countries: Botswana," Initiative on Public-Private Partnerships for Health, September 2004.
**144** "Botswana ARV Procurement and Supply Chain Management," Central Medical Stores, 2006.
**145** "Botswana: Country Overview," SCMS, viewed on August 15, 2011, http://scms.pfscm.org/scms/where/bw.
**146** Rook, Franziska, "Public-Private Partnerships in the Fight Against HIV/AIDS: A Case Study of Botswana," SPNA Review: Vol. 5, 2009.
**147** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**148** "Saving Lives: The ACHAP Experience in Botswana," ACHAP,
**149** "Botswana: PMTCT," UNICEF, 2010.
**150** UNAIDS database (extracted from http://www.aidsinfoonline.org/).

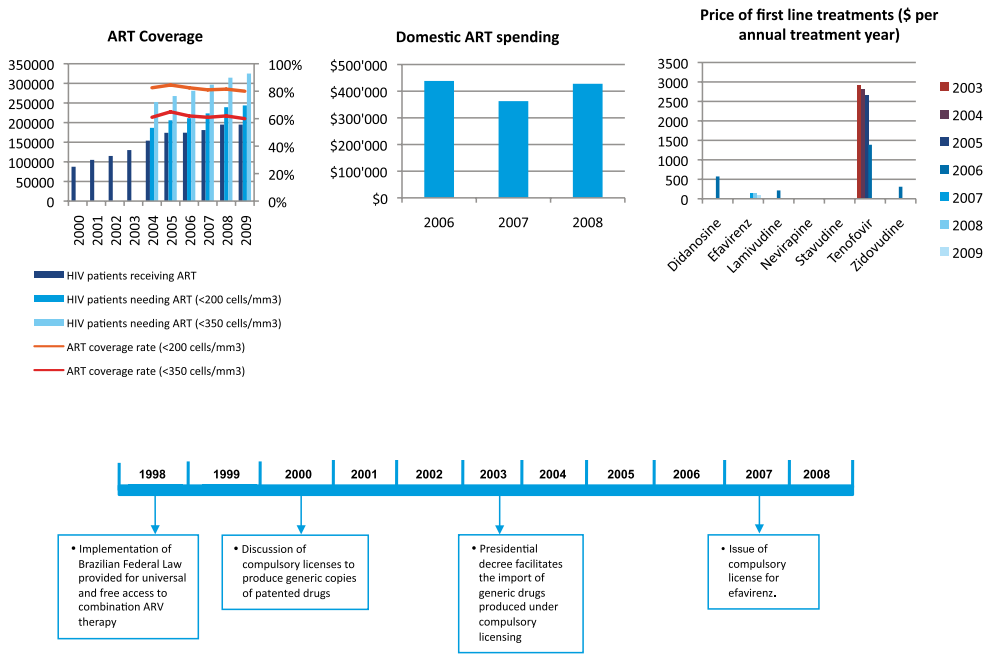
and is part of the second National Strategic Framework (2010-2016), which was approved in December 2009, as well as a primary objective of the second phase of ACHAP (2010-2014).

## 4.4.2 Brazil

Brazil has played a leadership role amongst developing countries in shaping global efforts to fight against the HIV/AIDS epidemic. Although HIV/AIDS prevalence among the general population in Brazil is not higher than in other neighbouring countries, in terms of the total number of people with HIV/AIDS, it is the second American country behind the US.

Figure 33: *Overview of Brazil*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




Brazil was one of the first countries to begin responding to the AIDS epidemic and develop access to ART. Indeed, the fight against the HIV/AIDS epidemic became a political priority in the late 80s, largely thanks to the presence of a very active civil society exerting pressure on public authorities. In particular, non-government organisations (NGOs) that were established in the late 1980s and in the early 1990s were integral in encouraging the government to adopt progressive AIDS policies.[151]

Brazil was a pioneer in challenging the predominant view during the 90s, which was that ARV treatment was not a cost-effective strategy in the developing world.[152] It was the first developing country to establish large-scale treatment

**151** Fonseca and Bastos (2007), "Twenty-five years of the AIDS epidemic in Brazil: principal epidemiological findings, 1980-2005", Cad Saude Publica, 23(3): 333-344.
**152** Nunn et al. (2009), "AIDS treatment in Brazil: Impacts and challenges", Health Affairs, 28(4)

programmes for HIV/AIDS patients. This truly began during health reform, the so-called 'sanitarista' movement, which successfully incorporated the universal right to healthcare in the 1988 Brazilian Constitution. Then, in 1996, Brazilian Federal Law provided for universal free access to combination ARV therapy. At the time, Brazil pioneered an integrated approach (prevention, institutional network capacity-building, social participation and provision of antiretroviral drugs), which UNAIDS and the WHO have recently stated was crucial in keeping the HIV/AIDS epidemic under control during the 90s.[153]

As an upper middle-income country, the main source of funding for Brazil's response to the HIV/AIDS epidemic has been domestic but between 1993 and 2007, Brazil received three loans from the World Bank to be used for strengthening its health system, training healthcare professionals, purchasing equipment and starting prevention campaigns.[154] Through the public health system (and financed by public funds), a network for diagnosis, prevention, treatment and follow-up was organised, which had 397 accredited hospitals, 79 day-care hospitals, 58 home-care centres and 422 outpatient facilities. All of the services provided by these facilities were provided free of charge to the public.[155]

The federal government financed the procurement of ARV drugs in the early 90s and in 1994 Brazil started producing the first generic ARV drug, AZT. By the end of 2009, of the 18 drugs that are provided in the public treatment programme, eight (zidovudine, stavudine, didanosine, lamivudine, ritonavir, saquinavir, indinavir and nevirapine) were manufactured domestically and ten were still imported. However, the share of originator companies has been increasing significantly through the decade.

Following the application of TRIPS, Brazil became one of the few countries to issue a compulsory licence for an ARV drug. While Brazil began threatening to issue compulsory licences to produce generic copies of patented drugs in 2000, only one compulsory licence has been issued by the Brazilian government in the name of health-related "public interest". It was for two pharmaceutical patents covering the imported ARV drug most used in HIV/AIDS treatment in the country — efavirenz (which was ultimately supplied through Indian generic manufacturers). However, most patented ARV drugs introduced in Brazil after 1996 are currently being supplied by the patent holders at prices negotiated by the Ministry of Health.

The number of HIV/AIDS patients receiving ART has increased steadily since the Brazilian government initiated its universal access programme in 1996. In 2000, 23% of the then HIV-infected population in Brazil were receiving ART. By the end of the decade, in 2009 the same figure was 31%, with 200,000 HIV/AIDS patients receiving ART and an estimated coverage rate of 80% according to the 2006 WHO guidelines. The success is attributable to an early focused political effort and the development of an integrated approach. The development of generics has also been a significant part of this success, as has negotiation with innovating companies. However, though it was only used in one instance, much of the attention Brazil gets in connection with HIV/AIDS is because of its use of compulsory licensing.

The most significant challenge that remains is to narrow regional differences

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**153** Galvao et al. (2008), "How the pandemic shapes the public health response — the case of HIV/AIDS in Brazil", in "Public Health Aspects of HIV/AIDS in Low and Middle Income Countries".
**154** However, the agreements with the World Bank did not allow using these loans to finance ARV treatment.
**155** Dirceu and Sima (2007), "Brazilian policy of universal access to AIDS treatment: sustainability challenges and perspectives", AIDS, 21(4).

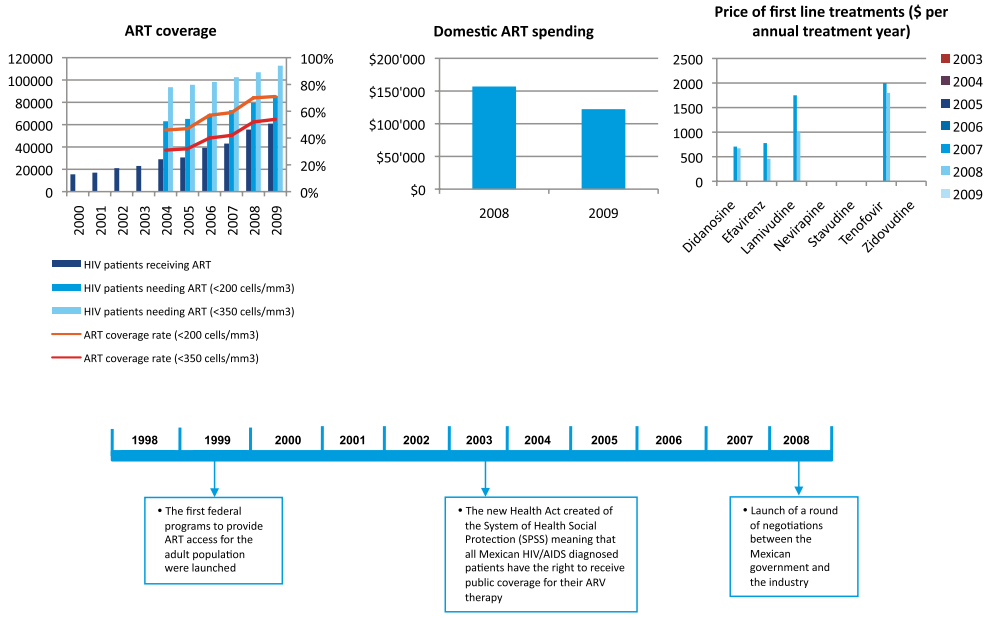
in access. Current facilities are heavily concentrated in the large metropolitan regions of the South and South-east, especially along the Rio de Janeiro — Sao Paulo corridor. The vast geographical extension of Brazil, the unequal economic development of Brazilian regions and the uneven distribution of people living with HIV/AIDS across the country continue to pose problems. Access to both treatment and prevention services need to be improved in remote regions of Brazil, and more effectively targeted at marginalised populations.[156]

### 4.4.3 Mexico

Mexico provides an example of an upper middle-income country with a concentrated epidemic that has been able to substantially improve access of HIV/AIDS patients to ARV drugs over the last decade, relying mainly on domestic resources.

Figure 34: *Overview of Mexico*

SOURCE: CRA DRAWING ON WHO COVERAGE DATA, UNAIDS SPENDING DATA IN $000S, GPRM




The efforts to increase ART access in Mexico have been led primarily by the Mexican government, without significant external contributions. The Mexican National Committee for AIDS Prevention and Control (CONASIDA) was launched in 1986 to coordinate public and private initiatives to fight against the HIV/AIDS epidemic in Mexico.[157] The committee has played an important role, in particular setting up the National Centre for HIV/AIDS Prevention and Control (CENSIDA) in 1988 as the main governmental agency to manage prevention and treatment

**156** Bastos et al. (2008), "AIDS in Brazil: the challenge and the response", in "Public Health Aspects of HIV/AIDS in Low and Middle Income Countries".
**157** Valdespino et al. (2008), "El diagnostico epidemiológico 1981-1995 y el primer Programa Nacional de Prevención: 1990-1994", in "25 años de SIDA en México: logros, desaciertos y retos".

of HIV/AIDS.[158] CENSIDA collaborates with other government entities as well as with NGOs, including organisations of persons living with HIV/AIDS. In 1999, the first federal programmes to provide ART access for the adult population were launched. Patients covered by social security institutions (mainly IMSS and ISSSTE) had enjoyed access to treatment since the late 90s. However, until the establishment of the System of Health Social Protection (SPSS) in 2003, a fraction of HIV/AIDS diagnosed patients did not have access to ART because they did not benefit from the social security scheme (over 40% of the population is not formally covered by any social security institution). With the creation of the SPSS, all Mexican HIV/AIDS diagnosed patients have been recognised the right to receive public coverage for their ARV therapy.

An important initiative undertaken by CENSIDA was the creation in 2005 of a network of centres specialised on HIV/AIDS, the Centros Ambulatorios de Prevencion y Atencion en SIDA e ITS (CAPASITS).[159] The CAPASITS are the result of collaboration between local governments, the national government and NGOs to provide comprehensive community-based treatment free of charge to people with HIV. The CAPASITS are still expanding throughout the country and have had an important impact in bordering states with larger vulnerable populations.[160]

Mexico's procurement of ARVs has always occurred through purchasing negotiations. Until the second half of 2008, prices of ARV drugs in Mexico were substantially higher than in other developing countries. This led to concerns about the sustainability of providing access as expenditures continued to increase, finally culminating in the launch of a new round of negotiations between the Mexican government and the industry during the second half of 2008. As a result of the negotiations, the prices of a number of ARV drugs were lowered considerably, implying negotiated price cuts of up to 40% for drugs like abacavir and efavirenz.[161]

Mexico has made substantial progress in providing access to ART for HIV/AIDS patients and the number of HIV/AIDS patients receiving ART has increased steadily over the last decade. Coverage has grown from 7,000 patients being treated in 1997 to 60,000 patients receiving ART in 2009. According to data from the Mexican National Centre for HIV/AIDS Prevention and Control (CENSIDA), universal coverage of diagnosed HIV/AIDS patients was achieved back in 2003. However, using the WHO definition, universal access has not yet been achieved.

Mexico illustrates the connection between HIV/AIDS and access to the entire healthcare system for the general population. Only after a system of universal coverage was adopted did access start to facilities improve. While the efforts led by the Mexican government over the past decade to increase coverage have proved very effective, new strategies must be developed to face the current challenges that the HIV/AIDS epidemic poses in Mexico. In the future, increasing numbers of HIV/AIDS patients being treated will translate into increasing treatment expenditures, and there will also need to be improvements in addressing late and under diagnosis (which is seen as one of the main bottlenecks impeding further improvements in ART coverage).

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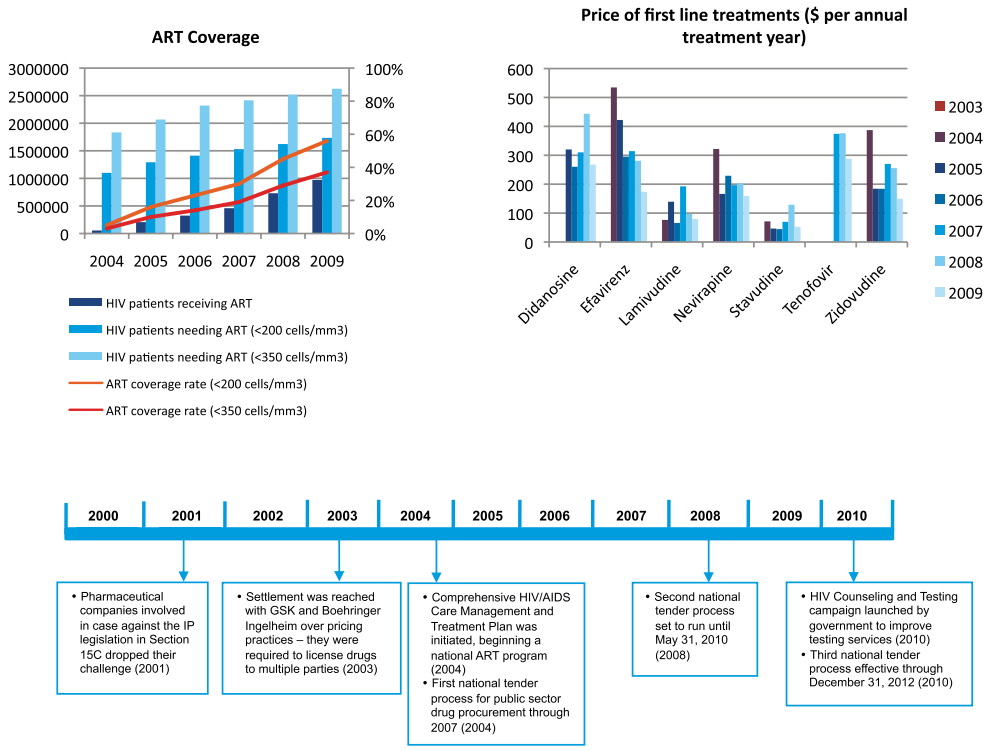
**158** http://www.censida.salud.gob.mx/
**159** http://www.censida.salud.gob.mx/interior/capasits.html
**160** http://aids-etc.org/aidsetc?page=rep-ummx-bg
**161** Calva Mercado and Vargas Infante (2009), "Cobertura universal con la terapia antiretroviral combinada. Logros y desafíos en la Secretaria de Salud de México", in "25 años de SIDA en México: logros, desaciertos y retos".

## 4.4.4 South Africa

South Africa, an upper middle-income country, has the world's largest epidemic, with approximately 5.7m people currently infected with the HIV virus and close to half a million people becoming newly infected each year.[162]

Figure 35: *Overview of South Africa*

SOURCE: CRA DRAWING ON WHO, UNAIDS,GPRM




While the HIV/AIDS epidemic was recognised by the South African government in the early 1990s, the initial government response was largely ineffective. There were several factors that explain the response of South Africa to the HIV/AIDS epidemic over the last two decades:

- The political upheaval occurring in the early years of the epidemic largely took focus away from the lack of access to ARVs while the new government initiated programmes focused primarily on prevention rather than treatment.

- Scepticism among a relevant part of the political class about the efficacy of ARV treatment had an impact on the approach of President Mbeki's government and in particular the Ministry of Health. As a consequence, there was no central government effort to provide ARVs during the 90s and the early 2000s. Many of the NGOs who were attempting to expand access to ARVs in South Africa felt alienated by the government initiatives, creating a divergent response.

162 UNAIDS database (extracted from http://www.aidsinfoonline.org/).

- Budget constraints constituted an obstacle to the implementation of large-scale ART programmes. Especially, because the South African government would refuse loans and sources of international aid available was still developing.

It wasn't until the beginning of 2004 that a comprehensive ART programme was rolled out. Civil society had a significant role in triggering this change of approach. In particular, the Treatment Action Campaign played a central role challenging government's positions legally in court. At that time, the Department of Health created a new Comprehensive HIV/AIDS Care, Management and Treatment Plan, which included a provision for all patients attending public health facilities with a CD4+ count <200 cells/mm$^3$ to receive ART.[163]

The South African government has been responsible for providing a large amount of the funds used. In 2006, public funds accounted for $425.9 million of HIV/AIDS spending and public spending has increased each year since then, accounting for $1.5 billion in 2009. International sources have also contributed significant amounts. In 2006, international sources provided support of $149.8 million and this grew to $570.0 million by 2009.[164] While it declined slightly as a percentage of total funding from 2008 to 2009, the South African government's funding still accounted for 72.7% of total funding in 2009.[165]

The procurement of ART medicines in South Africa has been contentious. In 2001-2003, an investigation into the pricing practices of pharmaceutical companies was conducted by the South African Competition Commission. The investigation was started after complaints and private lawsuits were filed by manufacturers of generics and public interest groups who were not satisfied with the level of price reductions that occurred during 2001. The intent of the lawsuits was to increase generic competition for ARVs, either through compulsory licensing or voluntary licensing. Ultimately, the Competition Commission found that GSK and Boehringer Ingelheim were in violation of antitrust laws because of their excessive pricing and refusal to license patents to particular generic manufacturers (they had refused to license patents to any manufacturers other than Aspen Pharmacare).[166] The settlement required GSK and Boehringer Ingelheim to allow select generic manufacturers to produce and sell some ARVs under a voluntary licence agreement in return for a royalty not to exceed 5% of sales of the ARV, much less than the 15-30% they had negotiated with Aspen Pharmacare.[167]

Since the ARV programme started in 2004, South Africa has used tender offers to purchase drugs for its public health system. Initially, the tender processes were seen to have a number of flaws (price rigidities resulting from three-year agreements implied the public sector could not always benefit from price reductions immediately).[168] Over time, the process has been significantly improved with increased transparency of drug costs and the ability to adjust pricing as market dynamics change.[169] Although predominantly supplied by generics, the largest

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**163** Johnson, Leigh, "Access to Antiretroviral Treatment in Adults," University of Cape Town, 2009.
**164** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**165** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**166** "The South Africa AIDS Controversy: A Case Study in Patent Law and Policy," Fisher and Rigamonti, February 10, 2005, p. 3. GSK also agreed to provide the AIDS clinics run by the AIDS Healthcare Foundation with ARVs at not-for-profit prices.
**167** "The South Africa AIDS Controversy: A Case Study in Patent Law and Policy," Fisher and Rigamonti, February 10, 2005, p. 3.
**168** "South Africa: Question Marks Over ARV Tender," PlusNews, March 10, 2008.
**169** "South Africa: How Better ARV Prices Were Won," African Crisis, January 21, 2011, http://www.africancrisis.co.za/Article.php?ID=89464&.

supplier of ARVs to the public sector in South Africa is Abbott, followed by domestic generic suppliers.[170]

Largely as a result of its delayed initiation of a universal treatment programme, access to ARVs in South Africa remains relatively low compared to other middle-income countries: 66% of people needing treatment actually received it in 2009 according to 2006 WHO guidelines (37% according to 2010 WHO guidelines).[171] When compared to other countries with similar income levels, it is clear that South Africa's response still lags behind other countries that started earlier. In a short period of time, a large population of people were initiated on ARVs, but the population of infected people was so large by this time that there was not enough capacity to provide universal coverage. In addition, there is large regional variation: the Western Cape has an estimated 68.2% of newly eligible adults starting treatment between 2007 and 2008 while Free State has had ARV coverage of only 27.5% in recent years.[172]

The South African experience illustrates how important it is to have a unified political response in order to expand access effectively. Local manufacturing and discounted ARV prices have contributed positively to access, but they are insufficient without government support. As in Mexico, achieving a high level of access is likely to require changes to the larger system of healthcare provision toward universal coverage.

Going forward, the government has proposed an aggressive schedule for increasing access to ARVs, which will require additional infrastructure, a large increase in the number of healthcare professionals and continuing education on the realities of HIV/AIDS and the benefits of ARV treatment.[173] The government also recently announced the provision of a national insurance fund that will ultimately provide coverage to the entire population.[174] In addition, the health minister recently confirmed that South Africa will begin offering ART to patients with CD4 counts below 350 cells/mm$^3$, rather than 200 cells/mm$^3$, as previously.[175]

## 4.5 LESSONS FROM THE CASE STUDIES

Examining the experiences depicted in the case studies, there are a number of clear themes that emerge regarding the effectiveness of interventions and the degree to which we can attribute improvement in access to individual policy decisions. For each of the interventions described in Chapter 3:

- Political will and a programme for universal access;
- Stigma, discrimination and social marginalisation;
- Domestic healthcare capacity;
- The role of international funding and support;
- Negotiation and procurement;

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**170** Department of Health
**171** UNAIDS database (extracted from http://www.aidsinfoonline.org/).
**172** Johnson, Leigh, "Access to Antiretroviral Treatment in Adults," University of Cape Town, 2009.
**173** "Expanding Access to ART in South Africa: The Role of Nurse-Initiated Treatment," South African Medical Journal, April 2010.
**174** "South Africa Unveils Universal Health Care Scheme," BBC, August 12, 2011.
**175** "South Africa Expands AIDS Program to Allow Earlier ARV Treatment," Kaiser Family Foundation, August 15, 2011.

- The entry of generic manufacturers;
- Compulsory licensing; and
- Public-private partnerships.

### 4.5.1 Political will and a programme for universal access

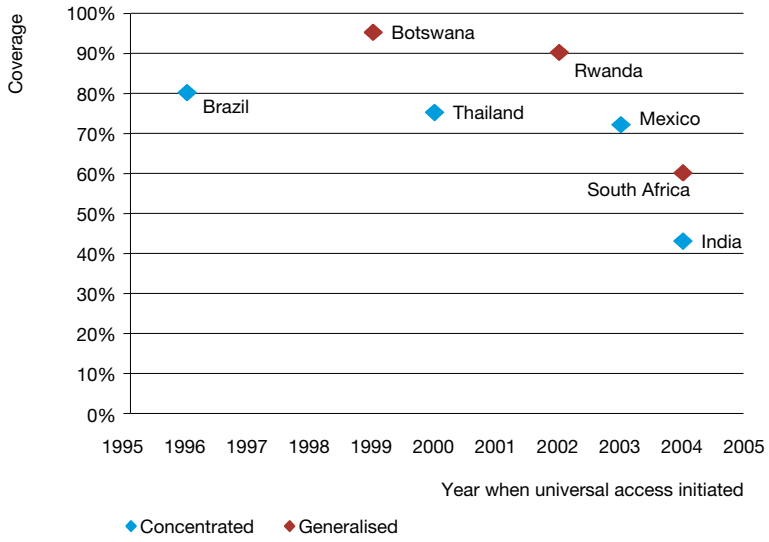
Political recognition of the epidemic and a strong commitment to address it is a critical part of the foundation for any sustained intervention programme. In some countries, providing universal coverage to ART became a significant political priority in the beginning of the 2000s or earlier, as was the case in Brazil and Botswana. The Brazilian government, in particular, committed to large-scale ART provision in the 90s, pushed by the activism of civil society and the rulings of native courts which recognised the constitutional right of HIV patients to receive free ART. In Botswana, where the prevalence rate of HIV/AIDS ranked amongst the highest in the world, the government was clear about its intention to fight against HIV/AIDS. The government's credible commitment was a determining factor in the decision by the Gates Foundation and the Merck Company Foundation to enter into partnership there.

In other countries, universal access to ART did not become a political priority until later. South Africa is a country where this occurred, with the political commitment not materialising until 2004, after many years of on-the-record government scepticism toward the use of ARVs.

As a result of the differences in political will between countries, there are large variations in the start dates of universal ARV programmes. It is hardly surprising that programmes starting earlier — in Brazil and Botswana — have been the most successful in achieving high levels of access to ARVs, while the countries with programmes that were not initiated until later have been forced to play catch-up throughout the last decade. In many cases, the countries not initiating their ARV programmes until later initially focused on prevention activities and were more sceptical about the effectiveness of ART. In these countries coverage rates have risen more slowly and have still not caught up with countries that focused on ART coverage in earlier years.

Figure 36: *Coverage in 2009 against year when universal access initiated*

SOURCE: WANING ET AL. (2010)[29]




## 4.5.2 Stigma, discrimination and social marginalisation

More than any other disease, responses to the HIV/AIDS epidemic have had to address problems associated with stigma and discrimination. This usually requires education campaigns that encourage patients to seek and maintain treatment. The case studies illustrate the need to address stigma and discrimination by changing the attitudes and behaviours of people working those living with HIV.

- Botswana: It is understood that there is widespread discrimination in Botswana against those people living with HIV/AIDS. This has manifest itself in a variety of ways, for example, women who are HIV positive and become pregnant tend to avoid preventing mother-to-child transmission services (PMTCT) because of the associated stigma and the abuse and discrimination they often receive from service providers. Addressing this has been important for increasing access. At the same time, increasing access can also lower stigmatisation. A study in Botswana found that stigmatising attitudes had lessened three years after the national programme providing universal access to treatment was introduced.[176]

- Brazil: Prior to introducing ART, Brazil had programmes that were oriented toward reducing stigma and exclusion, especially for vulnerable populations. NGOs and public health authorities cooperated in the implementation of programmes aimed at addressing this.[177]

- India: Hospital staff and health professionals have often been found to stigmatise HIV positive people in India. A study from 2006 found that 25% people living with HIV/AIDS in India have been refused medical treatment as a direct result of being HIV positive.[178]

**176** The study concluded that although improving access to antiretroviral treatment may be a factor in reducing stigma, it does not eliminate stigma altogether and does not lessen the fear of stigma amongst HIV positive people. Wolfe, W R et al (2008) 'The impact of Universal access to antiretroviral therapy on HIV stigma in Botswana
**177** Nunn et al. (2009), "Changing global essential medicines norms to improve access to AIDS treatment: Lessons from Brazil", Global Public Health, 4(2): 131-149.
**178** "The Socio Economic Impact of HIV and AIDS in India," UNDP, 2006.

- Rwanda: In the 1990s, there were prevention and education programmes, but the scepticism toward the effectiveness of HIV/AIDS treatment (in addition to other factors) slowed the initiation of a comprehensive treatment plan. Faith-based organisations (FBOs) have been particularly important in reducing stigma and discrimination in Rwanda. Many members of these organisations are affected by the virus and religious leaders are able to reach out to them in a supportive way, helping to eliminate negative stigmas and encouraging people to be tested.

- Mexico: The importance of addressing stigma associated with HIV/AIDS in order to improve treatment and adherence has been identified in recent academic analysis.[179]

- South Africa: It is recognised that stigma and confusion surrounding ART continues to persist today, and this has contributed to individuals avoiding diagnosis and/or treatment. However, the increase in access to ART has also helped to reduce stigma and discrimination.[180]

- Thailand: Studies including Thailand by WHO found that 34% of respondents reported breaches of confidentiality by health workers.[181]

Addressing negative stigmas associated with HIV/AIDS has been important in increasing access to treatment in all of the countries examined in this report. The problems that stem from these stigmas are in some ways dependent on the type of epidemic, and in particular the degree to which it is concentrated in populations that are the hardest to reach. In many countries, sex workers, injecting drug users, men who have sex with men, transgender people, prisoners and migrants are the populations where concentration levels are the highest, and the characteristics of those populations can influence the difficulty of achieving high levels of access to treatment.

It is perhaps no surprise that countries with concentrated epidemics (as illustrated in Figure 36) have not been able to achieve the highest levels of access. There is, however, little doubt that by improving education and reducing stigma, countries can reduce major barriers that exist for patients seeking out voluntary testing and treatment, which is critical for reducing the time to diagnosis and initiating effective treatment regimens.

### 4.5.3 Domestic healthcare capacity

Treating patients with HIV/AIDS is complex in the best of circumstances, but near impossible when there are fundamental weaknesses in the overall health system. Addressing the epidemic requires adequate human resource capacity (nurses, physicians and administrators), physical infrastructure, supply chains, health financing and information systems. Therefore, it is no surprise that the number and distribution of health facilities providing antiretroviral therapy are important determinants of access.

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**179** "Bridging the gap between antiretroviral access and adherence in Mexico". Campero L, Herrera C, Kendall T, Caballero M. SourceNational Institute of Public Health, Cuernavaca, Morelos, Mexico. Qual Health Res. 2007 May;17(5):599-611.
**180** "A comparison of HIV stigma and discrimination in five international sites: The influence of care and treatment resources in high prevalence settings" Suzanne Mamana Laurie Abler, Lisa Parker, Tim Lane, Admire Chirowodza, Jacob Ntogwisangu, Namtip Srirak, Precious Modiba, Oliver Murima, Katherine Fritz Social Science & Medicine (2009), doi:10.1016/j.socscimed.2009.04.002
**181** WHO (2008) 'Towards Universal Access: Scaling up priority HIV/AIDS interventions in the health sector: Progress report 2008'

Table 7: *Measures of healthcare strength*

SOURCE: WORLD BANK; DATA.WORLDBANK.ORG/TOPIC/HEALTH; WHO HTTP://APPS.WHO.INT/GHODATA/?VID=92000

| | Health expenditure per capita (current US$) | Number of physicians per capita |
|---|---|---|
| Botswana | 612 | 0.0003 |
| Brazil | 734 | 0.0017 |
| India | 45 | 0.0006 |
| Mexico | 515 | 0.0028 |
| Rwanda | 48 | 0.00002 |
| South Africa | 485 | 0.0007 |
| Thailand | 168 | 0.0003 |

With limited ability to provide diagnoses and offering and maintaining treatment, funding purchasing or providing the medicines by themselves do not increase access. Focusing purely on prevention or ensuring there are enough generic medicines is also not sufficient to contain the epidemic, as illustrated in India. In fact, even external funding and donations of ARVs in Botswana only increased access after the healthcare infrastructure was developed. Building up necessary infrastructure takes time and it is one of the primary reasons that countries struggle to raise access levels at an accelerated rate, being instead forced to raise access more gradually over time.

Table 8: *HIV testing facilities*

SOURCE: CRA ANALYSIS USING UNAIDS 2009, WHO, UNICEF

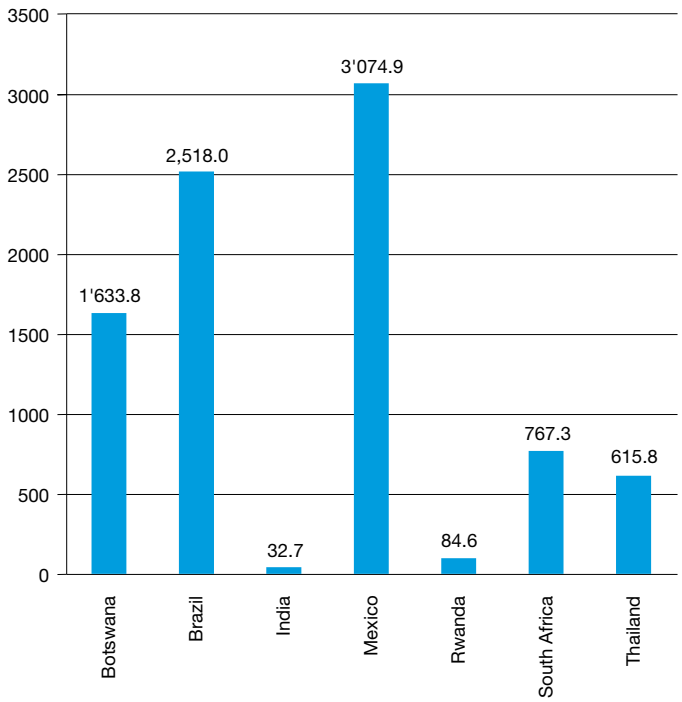
| | Number of facilities earlier in the decade | Number of facilities (2009) | Estimated number per 100,000 adult population | Estimate number per 1,000 of people in need ART |
|---|---|---|---|---|
| Botswana | 16 | 666 | 62.7 | 4.8 |
| Brazil | | 3,579 | 3.4 | 14.6 |
| India | 62 (1995)<br>4,269 (2007) | 5,089 | 0.8 | 6.9 |
| Mexico | | 2,784 | 4.7 | 32.4 |
| Rwanda | 44 (2003)<br>223 (2005) | 395 | 8 | 5.5 |
| South Africa | | 4,326 | 15.8 | 2.5 |
| Thailand | | 1,014 | 2.7 | 3.5 |

The strength of the overall health system varies significantly within our case studies. As would be expected, more wealthy countries, such as Brazil and Mexico, have stronger health systems. This does not mean, however, that these countries do not suffer from structural weaknesses that limit their capacity to manage large-scale ART programmes. An insufficient number of healthcare facilities and a lack of adequate training for healthcare professionals remain problems. As set out in Table 8, there is wide variation in the provision of HIV testing across the case study countries. However, even countries with relatively poor overall health systems, such as Rwanda, have seen significant increases in HIV testing facilities.

The differences in provision of ART are inevitable when we consider the huge differences in each country's ability to finance domestic spending on HIV as illustrated in Figure 37.

Figure 37: *Domestic spending on HIV - Total reported domestic public expenditure million USD per person needing ART*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

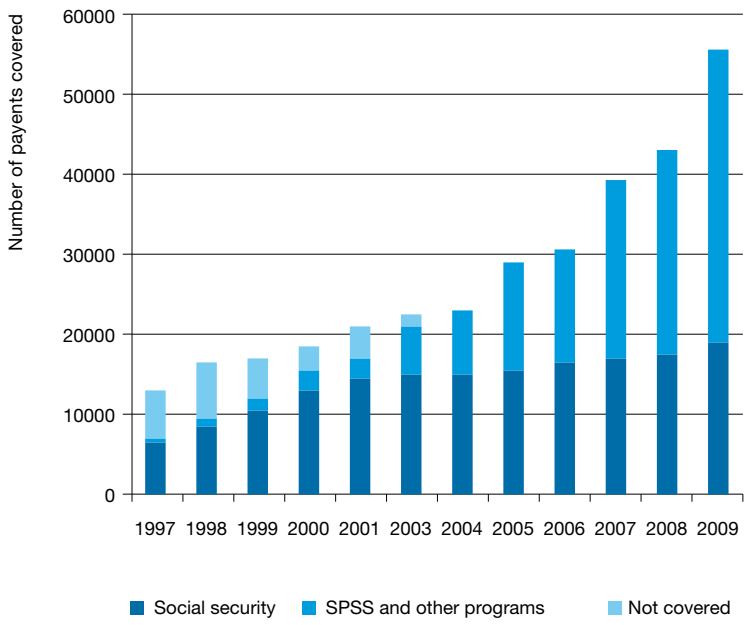



Countries with concentrated epidemics also suffer from weaknesses in their healthcare systems. Vulnerable populations in these countries are often hard-to-reach populations, meaning that the health system may struggle to offer them adequate testing, diagnosis and treatment. This is the case for certain vulnerable migrant populations in Mexico, whose mobility and social exclusion makes healthcare provision more difficult. In Brazil, the concentration of healthcare facilities in urban areas contrasts with the lack of infrastructure in the Northern rural areas.

In addition to the provision of healthcare, patients most vulnerable to the disease need to be able to afford treatment. In middle-income countries, such as Mexico, improvements in access have only been achieved since universal health insurance coverage has been achieved. In this case, the increase in ART coverage rate has mirrored the increase in healthcare coverage, as illustrated in Figure 38.

Figure 38: *Provision of HIV coverage in Mexico*

SOURCE: CALVA MERCADO AND VARGAS INFANTE (2008)




Integrated HIV/AIDS strategies that include activities for prevention, treatment and care that are developed as national plans appears to be present in the majority of countries that were examined in this study. The early adoption of an integrated plan is a primary reason for the success of Brazil in managing the epidemic.[182]

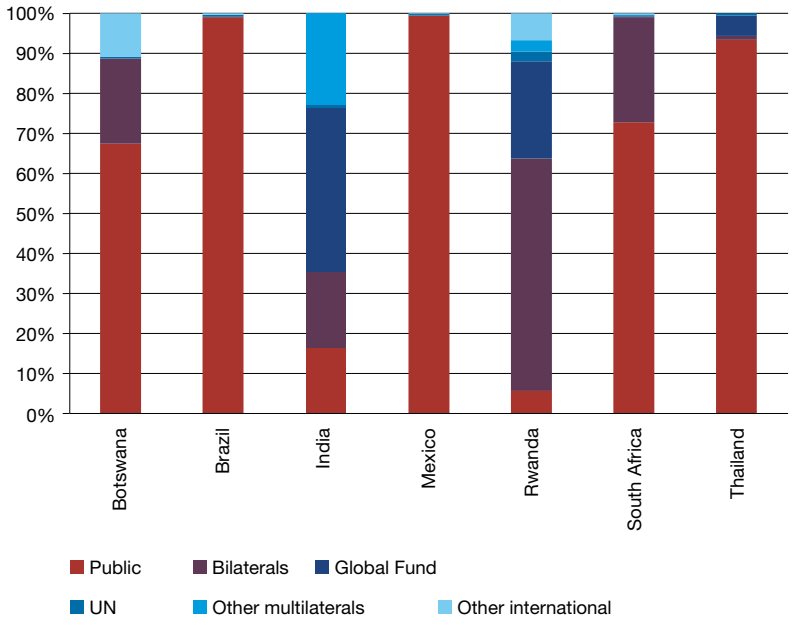
## 4.5.4 The role of international funding and support

The case studies illustrate how the role of the international community in funding of HIV/AIDS varies largely as a result of the income level in each country. As shown in Figure 39, low-income countries have been more dependent on international support. For example, in Rwanda, more than 90% of HIV/AIDS spending in 2009 came from external sources. Most of the funding was received through bilateral channels, although there was also a significant presence from multilateral organisations, and in particular the Global Fund.

**182** We are referring to integration of prevention, treatment and care but it clearly important to integrate other diseases into the HIV strategy, with HIV-related tuberculosis (TB) remaining a serious challenge.

Figure 39: *Source of funding for HIV/AIDS spending in 2009*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

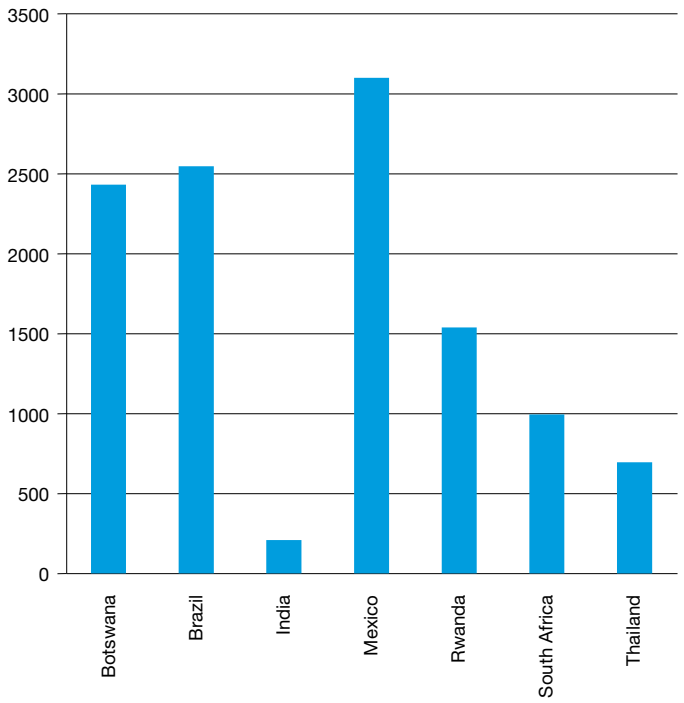



The other two SSA countries, Botswana and South Africa, also received substantial amounts of international aid, which represented around 30% of HIV/AIDS spending. While South Africa received bilateral aid, Botswana received substantial aid from other sources, primarily from the public-private partnership between the Gates Foundation, the Merck Company Foundation and Botswana's government. Due to the generalised epidemic they face, SSA countries have access to international funding even when they have relatively high levels of average income.

Lower middle-income countries with concentrated epidemics have limited access to international funding, such as is the case for Thailand. Upper middle-income countries with concentrated epidemics, such as Brazil and Mexico, have little to no access to international funding for HIV/AIDS. However, even though they receive less funding from external sources, middle-income countries still spend considerably more on HIV/AIDS than lower income and lower middle-income countries. As illustrated below, the impact of international funding has been to bring the lower income countries closer to the lower middle-income countries.

Figure 40: *Total spending on HIV — Total reported domestic public and international expenditure million USD per person needing ART*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)




However, examining only the funding of ARVs or HIV testing is an overly simplistic method for assessing the role of the international community. Assistance has also contributed to:

- Improvements in the overall health system (as illustrated by the loans from the World Bank in Brazil);
- Assistance in procurement efforts, logistical support and supply chain management to prevent drug stock-outs and shortages; and
- Provision of technical support to national partners.

Even in low-income countries, the role of international spending has also served more indirect but equally important purposes. For example, in Rwanda, the Coordinated Procurement and Distribution System for antiretrovirals and drugs for opportunistic infections brings together government officials, donors, national institutions and international organisations to improve the supply chain for ARVs. This has succeeded in reducing stock-outs and drug expiry by ensuring that once potential antiretroviral stock-outs are identified, other sources can step in to fill the gaps.[183]

The substantial increase in resources from the international community that has been dedicated to promoting health over the last several years has begun to change the trajectory of the HIV/AIDS epidemic, as evidenced by the case

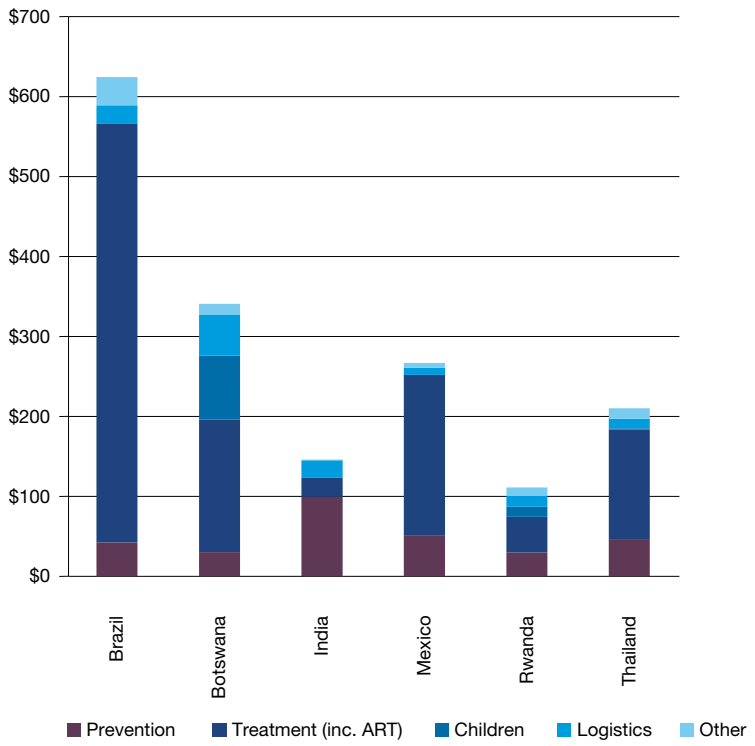
**183** UNAIDS (2010), "Towards Universal Access: Scaling up priority HIV/AIDS Interventions in the health sector"

studies of Rwanda, Botswana and South Africa. Only once the Global Fund, PEPFAR, the Gates Foundation, the Clinton Foundation and UNAIDS focused resources did access start to improve for the poorest countries. Middle-income countries have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit.

The use of HIV funding varies substantially across our case study countries. The relative emphasis put on prevention and treatment, in particular, has been different. As shown in Figure 41, India stands out as having chosen to prioritise prevention at the expense of ART, while all other countries spend the largest share of their funds on providing ART.

Figure 41: *Use of HIV expenditure in 2009 (in millions US$)*

SOURCE: UNAIDS DATABASE (EXTRACTED FROM HTTP://WWW.AIDSINFOONLINE.ORG/)

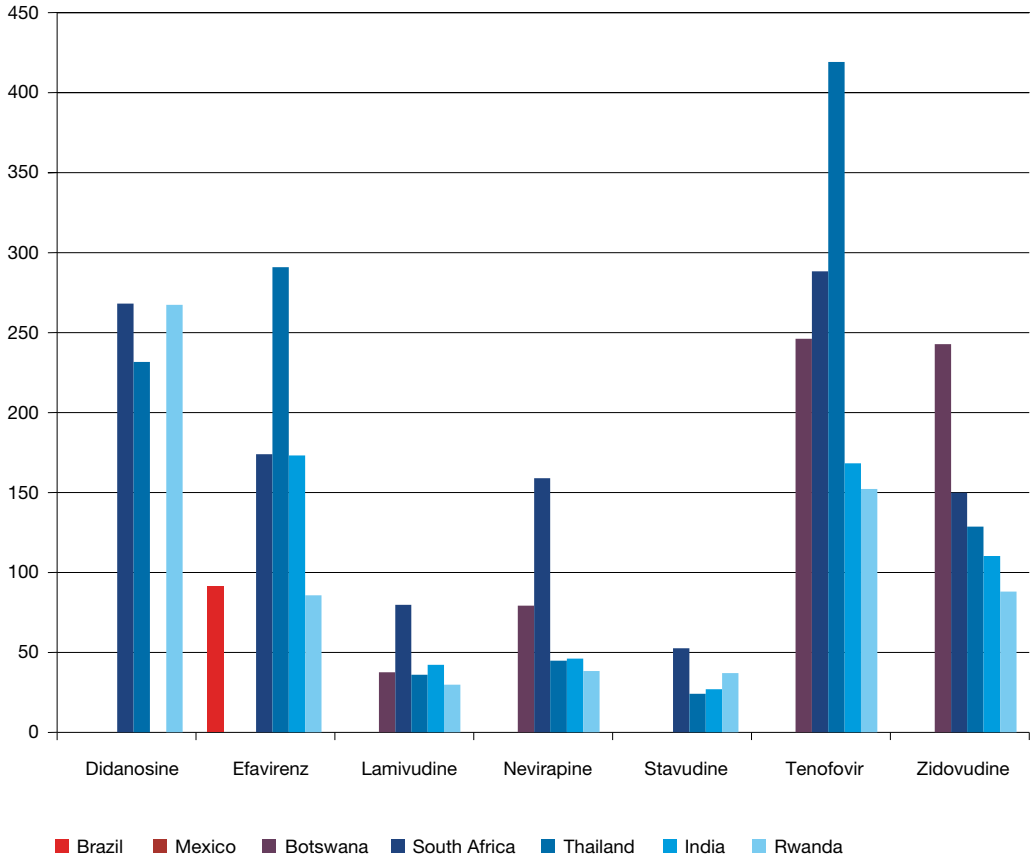



## 4.5.5 Negotiation and procurement

In each of the markets considered there were, and continue to be, concerns regarding the price of ART and its affordability. In all of the case studies, the price of first-line ART fell significantly during the decade. However, as illustrated in Figure 42, prices still vary significantly between these countries. The relationship between prices and the income level of each country varies from product to product — although generally lower income countries have lower prices. It is also noticeable that the older the medicine the narrower the set of prices (investigated further in the next chapter).

Figure 42: *Price of first-line treatments*

SOURCE: CRA BASED ON GPRM




This is likely to reflect a number of factors, among which are the use of differential pricing schemes and different procurement mechanisms.

**Differential pricing**

Differential pricing schemes for ARV drugs have been developed by most pharmaceutical companies. Each country has its own position regarding their access to differential pricing schemes depending on their income level and the state of their epidemic. Rwanda is a low-income country with a high degree of prevalence, so it has access to the lowest prices. Botswana and South Africa also generally have access to the lowest prices because they are SSA countries with large epidemics. Brazil, Mexico and Thailand are middle-income countries with concentrated epidemics; hence they do not usually have access to the same pricing arrangements as the countries named above. However, they are still usually offered discounted pricing.

Differential pricing was developed in 2000/2001. For most pharmaceutical companies, not-for-profit prices have been offered for least developed countries

and sub-Saharan Africa.[184] Companies often negotiate pricing arrangements for HIV/AIDS medicines with middle-income countries on a case-by-case basis. The categorisation of our case studies in the differential pricing schemes of different originator companies is set out in Table 9.

Table 9: *Access to differential price schemes*

SOURCE: UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS;
WHERE CATEGORIES ARE DEFINED BY THE COMPANIES WITH CATEGORY 1 OFFERING PREFERENTIAL PRICES COMPARED TO CATEGORY 2

| | Abbott | BMS | Boehringer Ingelheim | Gilead | Merck & Co. | Roche | Tibotec | ViiV |
|---|---|---|---|---|---|---|---|---|
| **Botswana** | Category 1 | Category 2 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 |
| **Brazil** | Category 2 | | Category 2 | | | | Category 2 | Category 2 |
| **India** | Category 2 | | Category 2 | Category 1 | | | Category 2 | Category 2 |
| **Mexico** | | | Category 2 | | | | Category 2 | Category 2 |
| **Rwanda** | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 |
| **South Africa** | Category 1 | Category 2 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 | Category 1 |

In practice, differential pricing often results from negotiation, and access to various price points can change as the epidemic evolves. This point is illustrated by observing the process in Mexico. As a result of the steep increase in the number of patients receiving ART in Mexico, and especially the growing number of patients receiving medicines funded by the government through the SPSS, there was a dramatic increase in expenditures for ARVs. Concerns about the sustainability of these expenditures led to the launch of a round of negotiations between the Mexican government and the industry during the second half of 2008. As a result of the negotiation, the prices of a number of ARV drugs were lowered considerably, implying negotiated price cuts of up to 40% for drugs like abacavir and efavirenz.[185] Table 10 reports the price reductions agreed in the negotiations in 2008.

**184** For example, GSK's strategy is set out in http://www.gsk.com/responsibility/downloads/GSK-CR-2010-Report.pdf
**185** Calva Mercado and Vargas Infante (2009), "Cobertura universal con la terapia antiretroviral combinada. Logros y desafíos en la Secretaria de Salud de México", in "25 años de SIDA en México: logros, desaciertos y retos".

Table 10: *Price reductions in Mexico after the 2008 negotiation*

SOURCE: CALVA MERCADO AND VARGAS INFANTE (2008)

| Drug | Company | Price before negotiation | Price after negotiation | Price reduction |
|---|---|---|---|---|
| Lopinavir/ritonavir (sol.) | Abbott | 2601.00 | 2601.00 | 0 % |
| Lopinavir/ritonavir | Abbott | 4688.00 | 3750.40 | 20 % |
| Ritonavir | Abbott | 2368.00 | 2368.00 | 0 % |
| Nevirapine (sol.) | Promeco | 473.28 | 369.16 | 22 % |
| Nevirapine | Promeco | 389.00 | 389.00 | 0 % |
| Tipranavir | Promeco | 4854.78 | 4369.30 | 10 % |
| Atazanavir | Bristol | 3603.21 | 2878.86 | 20 % |
| Didanosine 250mg | Bristol | 706.20 | 670.89 | 8 % |
| Didanosine 400mg | Bristol | 1135.29 | 1078.53 | 7 % |
| Abacavir (sol.) | GSK | 964.55 | 578.67 | 40 % |
| Abacavir | GSK | 2364.66 | 1418.80 | 40 % |
| Abacavir/lamivudine | GSK | 3000.00 | 2250.00 | 25 % |
| Lamivudine (sol.) | GSK | 919.90 | 919.90 | 0 % |
| Lamivudine | GSK | 1750.00 | 1000.00 | 43 % |
| Lamivudine/zidovudine | GSK | 2568.89 | 2055.11 | 20 % |
| Fosamprenavir | GSK | 3569.64 | 2747.19 | 23 % |
| Efavirenz | MSD | 777.72 | 458.85 | 41 % |
| Raltegravir | MSD | 8000.00 | 6581.00 | 17 % |
| Enfuvirtide | Roche | 23892.30 | 20308.46 | 15 % |
| Saquinavir | Roche | 2637.00 | 2452.00 | 7 % |
| Emtricitabine | Stendhal (Gilead) | 1000.00 | 1000.00 | 0 % |
| Tenofovir/emtricitabine | Stendhal (Gilead) | 3000.00 | 2312.00 | 23 % |
| Tenofovir | Stendhal (Gilead) | 2000.00 | 1800.00 | 10 % |

**Procurement mechanisms**

Countries have used different procurement vehicles to negotiate lower prices, including pooled procurement. In the case studies, various procurement strategies have played an important role in lowering prices in each country:

- Botswana works with PEPFAR to purchase ARVs. PEPFAR provides support to ensure a safe and secure supply of ARVs by procuring the drugs and providing training on supply chain management, quality assurance, good manufacturing practices, inspections and pharmacovigilance.[186]

- South Africa has used a centralised tender process since 2004, and it has achieved significant cost reductions. Following the recent success in negotiating a better deal on HIV/Aids drugs, the health department has taken over responsibility for tenders from the Treasury. The change will involve the health department setting up its own central procurement unit using financial funding support from the Global Fund.[187]

- Rwanda initially relied on group purchasing from the Clinton Foundation to supply its ARV programme. Then, in October 2004, the Rwandan Ministry of Health issued a Ministerial Order that required all ARVs to be procured by the Centrale d'Achats des Médicaments Essentiels Consommables et Equipements Medicaux du Rwanda (CAMERWA), a national agency for pharmaceutical procurement.

- In South Africa, there have been a number of studies showing how the prices achieved in their tender process compare to international prices. This analysis has involved comparing the prices attained by South Africa with the lowest prices listed in the International Drug Price Indicator Guide (IDPIG).[188] The results show that South Africa has been buying at prices similar to the lowest prices internationally — although the most recent study notes that international prices for a number of products have fallen significantly in recent years.

- In Thailand, ARV drugs that are not manufactured by the domestic public industry are purchased from foreign suppliers. Procurement is organised centrally by the National Plan for HIV/AIDS, both for domestically financed ARV drugs and for those supported through Global Fund grants.

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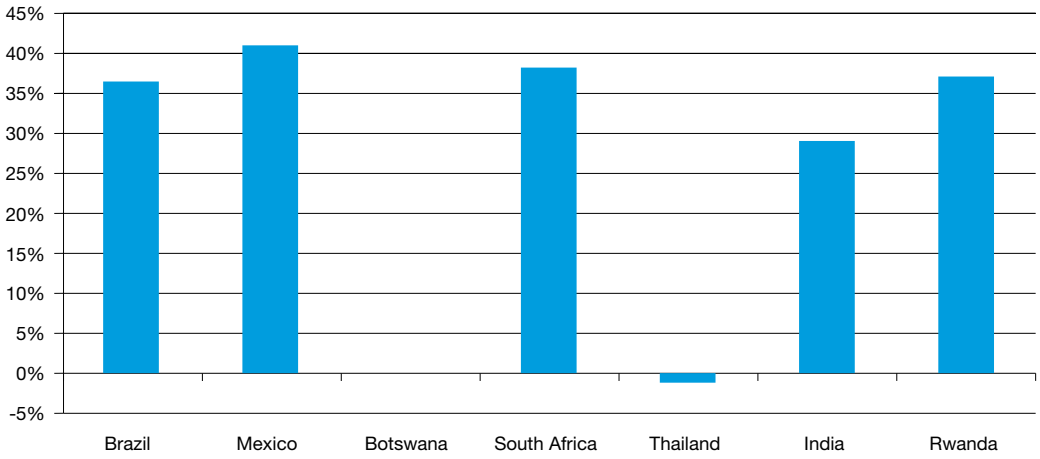
**186** http://www.pepfar.gov/about/82468.htm
**187** http://www.cmp.co.za/news-articles/Latest/department-of-health-to-take-over-medicine-tendering
**188** PIASA Tender Price Analysis

Figure 43: *Price reduction for Efavirenz 2008/9*

SOURCE: CRA BASED ON GPRM & LOCAL STUDIES




Each of these models of procurement has had success reducing prices. Although paying different prices for medicines, Figure 43 illustrates that different negotiation and procurement mechanisms can achieve price reduction.

However, in addition to negotiating with patent owners, an important component of lower prices has been the introduction of generic ARVs, either as a result of patent expiry, licensing arrangements or, in several cases, compulsory licensing. We turn to these in the next section.

## 4.5.6 The entry of generic manufacturers

The entry of generic manufacturers has been important in several of the case studies. It is, however, useful to distinguish the situation in different countries and between first-line treatments and second-line treatments.

The least-developed countries were not obliged to implement the TRIPS agreement with respect to pharmaceutical products. Similarly, patents are not an issue in access to drugs in SSA countries, since most drug companies have not obtained patents widely in Africa.[189] This is, for instance, the case in Rwanda. In addition, procurement agencies working for PEPFAR or countries' health programmes purchase generic medicines.

In middle-income countries (not included in the least developed country category) ARV medicines were under patent protection, and only beginning in 2006 did the 20 years of patent protection expire for the three medicines that were developed first.[190] However, the transition period allowed within the TRIPS means that existing generic products on the market when the country

**189** "Patent protection and access to HIV/AIDS pharmaceuticals in sub-Saharan Africa" A report prepared for the World Intellectual Property Organisation (WIPO)

**190** "The three drugs are didanosine (ddI), zalcitabine (D4T) and zidovudine (AZT)." Please see: P. Boulet, J. Perriens, F. Renaud-Théry / Joint UNAIDS/WHO publication, "Patent Situation of HIV/AIDS-related drugs in 80 countries (2000)". Online: http://www.who.int/medicines/library/par/hivrelateddocs/patenTShivdrugs.pdf; Also see Pascale Boulet, Christopher Garrison and Ellen 97 t Hoen, "Drug Patents Under the Spotlight — sharing practical knowledge about pharmaceutical patents" Medecins Sans Frontieres, May 2003. See Annex A — Patent Table." Online: http://www.aerzte-ohne-grenzen.de/_media/1256__msf

implemented TRIPS could continue to be marketed and sold. In our cases studies they implemented TRIPS accordingly:

- Brazil — Brazil's Industrial Property Law (Law Nº 9.279, of May 14, 1996) was revised in accordance with the TRIPS Agreement in 1996 and came into force in May of 1997.
- Thailand — On 1st January 1995, Thailand became a party to GATT and the WTO and thus became bound by the associated TRIPS Agreement.
- India — Patent legislation finally became TRIPS compliant on January 1, 2005.
- Mexico — The Mexican IP environment has gradually changed over the last 20 years, starting with the Law for the Development of Industrial Property in 1991 (which initiated patent protection of pharmaceutical products patents) and progressing with the country's accession to various international Treaties including the North American Free Trade Agreement (NAFTA in January 1994, with the USA and Canada) and Trade Related Aspects of Intellectual Property Rights (TRIPS in January 1995, as part of Mexico adhering to GATT and the associated World Trade Organisation agreements).[191]

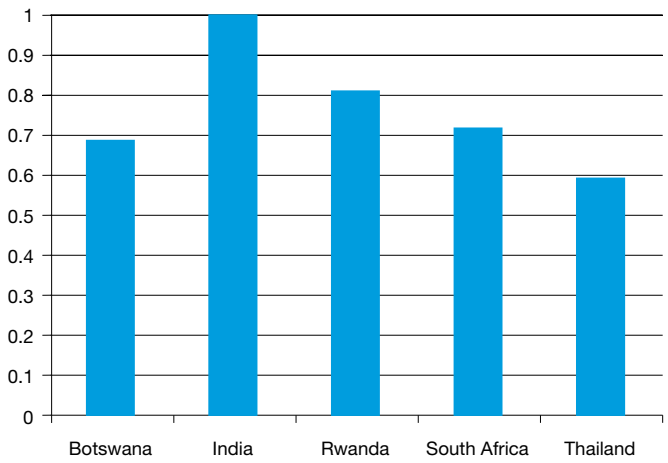
This means that less expensive generic versions of some of the patented ARV medicines could be produced legally, as a result of differences in the domestic intellectual property schemes that existed in some countries prior to compliance with TRIPS. It is clearly the case that this does not apply to medicines that were discovered later and therefore have remained under patent protection for several years in middle-income countries.

Among our case studies, all but Mexico have made significant purchases of ARV medicines from generic manufacturers, either domestic or foreign. Looking at low- and middle-income countries as a whole, data from the WHO Global Price Reporting Mechanism can be used to obtain an estimate of the share of the market that is supplied by generic manufacturers. Figure 44 reports the generic market share for a number of ARV medicines between 2005 and 2009.

**191** World Intellectual Property Organisation legal resources, "Mexico". Available at http://www.wipo.int/wipolex/en/results.jsp?countries=MX&cat_id=1

Figure 44: *Generic market shares in case study countries for the period 2005-2009 (ddd volume share) covered by GPRM database*

SOURCE: CRA BASED ON GPRM



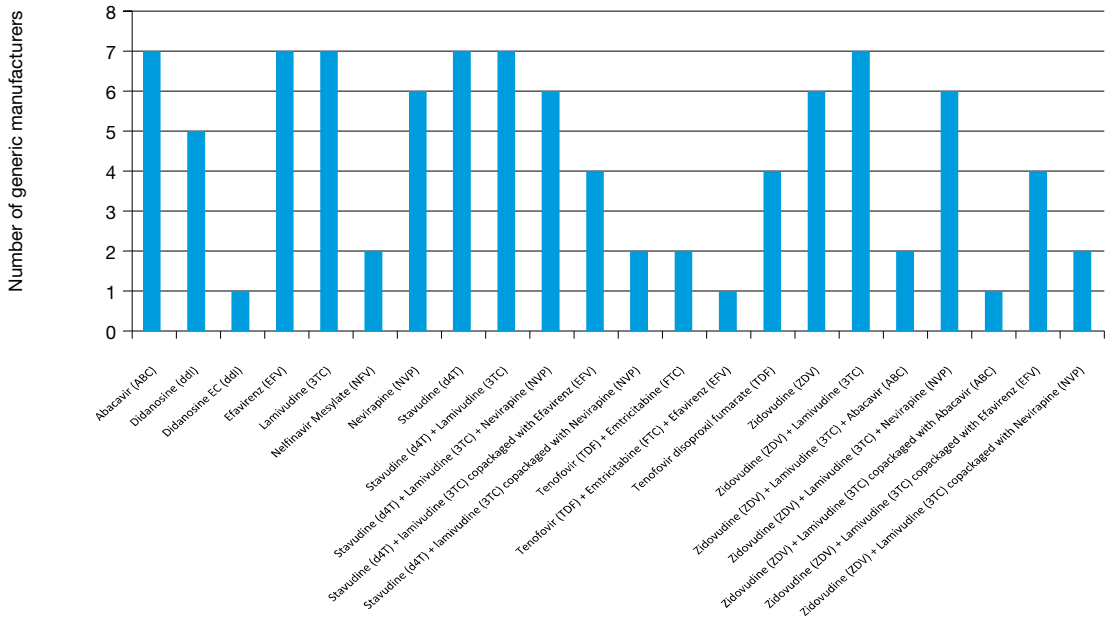

**The importance of Indian generics**

Generics manufacturers are able to offer reduced prices of medicines as they do not need to recover the cost of developing the medicine and they can by exploit specialisation and economies of scale. This has been a major factor in improving the affordability of universal access programmes in the poorest countries. Although some of the case studies have a domestic generic industry (South Africa, Thailand and Brazil), the development of the Indian generic industry has been an important component of increased access. Indeed, the current WHO list of prequalified ARV drugs contains 108 formulations:

- 88 correspond to Indian producers;
- 7 correspond to South African producers;
- 1 corresponds to a producer in Zimbabwe; and
- 20 correspond to formulations produced in developed countries by branded producers.
- Cipla, Matrix and Ranbaxy are the main prequalified Indian generic producers and Aspen is the only one in South Africa. However, there are many generic competitors in India for each of the main first-line medicines, as illustrated in Figure 45.

Figure 45: *Number of generics for first-line ARV drugs*

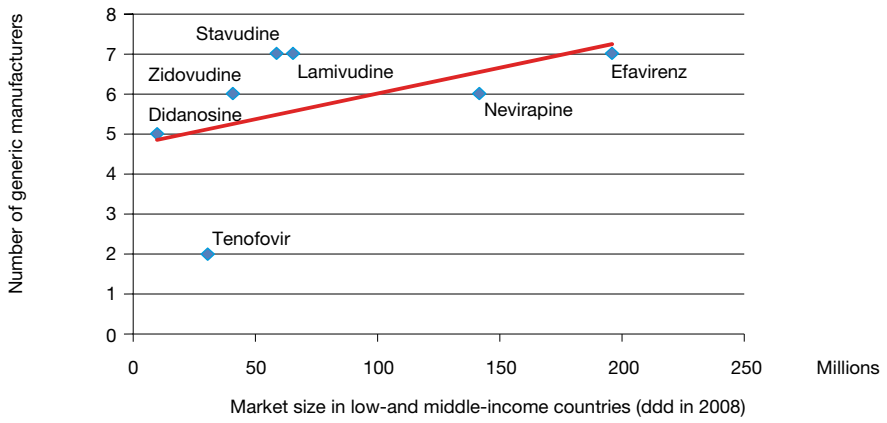
SOURCE: WHO DRUG REGULATORY STATUS DATABASE; CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES, «UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS,» 2010.




The number of generic manufacturers appears related to the size of the market. In Figure 46 we look at this relation for a number of first line ARV drugs. The number of generic manufacturers appears to be correlated with the size of the market. Moreover, those drugs with a higher number of generic manufacturers are also those that were introduced earlier in the market, like stavudine or zidovudine. This is consistent with these older drugs currently being in decline, but having been able to attract generics in the past, when they were more intensively used. This analysis must be interpreted with care, because it does not include fixed dose combinations (FDC). However, to the extent that the market size of the single drugs is positively correlated with the markets size of the corresponding FDC, the conclusion remains valid.

Figure 46: *Relation between market size and number of generic manufacturers*

SOURCE: CRA BASED ON GPRM AND WHO DRUG REGULATORY STATUS DATABASE




Unsurprisingly, the provision of Indian generics has been important in the provision of ARVs in India, however, only once the universal service programme was initiated. It has also been important in the provision in markets without their own generic ARV manufacturers, such as Botswana and Rwanda.

**Domestic manufacturers in Brazil, South Africa and Thailand**

In Brazil, South Africa and Thailand both domestic and Indian manufacturers have been important.

In Brazil, generic ARV drugs are produced by a number of federal and state laboratories, the most significant being the federal public laboratory, Far Manguinhos.[192] The domestic industry is an important supplier of ARV: around 40% of ARVs purchased by the government were manufactured domestically in 2006.[193] Several ARVs that are produced generically in Brazil were patented before the TRIPS agreement, which means that they can legally be copied.[194] We can identify three situations:

- With respect to older ARV medicines that were not patented in Brazil prior to 1997, such as stavudine and zidovudine. These ARV medicines were produced legally and in accordance with the TRIPS Agreement, because they are first-line antiretroviral generics that were patented internationally prior to 1997.

- Newer drugs such as lamivudine, nelfinavir, efavirenz, lopinavir+ritonavir, and ritonavir, received patent protection in Brazil because of special pipeline protection.[195]

**192** "Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand"
**193** Wise J. (2006), 'Access to AIDS medicines stumbles on trade rules', Bulletin of the World Health Organisation, Volume 84, Number 5, May 2006, 337-424
**194** Okie S. (May 2006), 'Fighting HIV — lessons f9=om Brazil', The New England Journal of Medicine 354;19
**195** Article 230 of the Industrial Property Law authorises protection for products that were patented protection prior to 1997 if they meet two criteria: they received patent protection in another country and also had not been marketed previously in Brazil. Supra note 6 (MSF Annex A)

- Several other ARV medicines were either not eligible or did not file for pipeline protection. They include for instance: delaviridine, didanosine, nevirapine, zalcitabine and indinavir.[196] Therefore it was possible for Brazilian manufacturers to produce these or Indian generics to be imported.

The Industrial Property Law introduced patent rights for pharmaceuticals in Brazil, guaranteeing drug companies exclusive marketing rights for their products. Although in principle it limited government production of generic drugs to those introduced in the Brazilian marketplace before 1997,[197] in practice a wider set of medicines has been produced.

For many first-line products, Brazil has developed its own generic manufacturer. However, it is important to note that this has often been based on the production of active principle ingredient (API) in India. Indeed, the economies of scale that Brazil offered through purchasing API is attributed to encouraged Indian firms to enter the market, thereby increasing competition and driving costs down.[198]

In 2003, seventeen national manufacturers were producing generic ARV medicines in Brazil, including the one federal producer, Far-Manguinhos mentioned above, and sixteen state-owned companies.[199] The number of national companies is now apparently around 27 out a total of 56 generic companies in Brazil.[200]

It is clearly the case that Brazilian generics lowered the price of ARV drugs in Brazil. There is some debate as to whether prices got as low as they would have with Indian generics.

While generic ARV drugs have played a role in Brazil's effort to provide ART treatment, a significant share of ARV drugs are supplied by the branded producers. Brazil is unable to legally produce generic versions of all of first-line ARV medicines. In 2005 Brazil imported seven of the fifteen ARVs distributed by the Ministry of Health.[201]

For those products that were patented (with the exception of those compulsory licensed), the Brazilian government needed to negotiate with the manufacturer. Indeed, most patented ARV drugs introduced in Brazil after 1996 are currently supplied by the patent holders at prices negotiated with the Ministry of Health. Table 11 shows price declines in Brazil for a number of products launched since 1998. Patent products such as lopinavir/ritonavir and tenofovir have seen significant price reductions. While price reductions were observed for a diverse set of products, including first- and second-line treatments, the prices of second-line treatments remain higher than those of first-lines. This is, for instance, the case for the protease inhibitors atazanavir and lopinavir+ritonavir, compared to the NNRTIs in the table.

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**196** Supra note 6 (MSF Annex A)
**197** "AIDSTreatment In Brazil: Impacts And Challenges" HEALTH AFFAIRS ~ Volume 28, Number 4
**198** Nunn A, (2009), 'AIDS Treatment in Brazil: Impacts and Challenges', Health Affairs 28(4)
**199** James Love, "Brazil Considers Compulsory Licenses, Defends Doha P6 Deal" IPS news article, September 6, 2003.
Online: http://lists.essential.org/pipermail/ip-health/2003-September/005237.html
**200** See footnote 38
**201** BBC News, "Brazil to Break AIDS Drug Patents" Dec 1, 2004
Online: http://news.bbc.co.uk/go/pr/fr/-/2/hi/health/4059147.stm; see note 40 for a list of drugs that Brazil can produce.

Table 11: *Price reductions in Brazil (US$)*

SOURCE: NUNN ET AL. (2007)

| Drug | First offer price | First launch price | Last recorded price | Decline from first offer price | Decline from first launch price |
|---|---|---|---|---|---|
| Atazanavir | 10,074 | 2,373 | 2,190 | 75% | 8% |
| Efavirenz | 2,540 | 2,540 | 577 | 77% | 77% |
| Nelfinavir | 5,585 | 5,585 | 1716 | 69% | 69% |
| Lopinavir/ritonavir | 6,504 | 4,139 | 1,022 | 84% | 75% |
| Tenofovir | 5,037 | 3,296 | 1,387 | 72% | 58% |

The development of the South African domestic production of generics differed considerably from the Brazilian case. Prior to mid-1990s there was not a significant industry in South Africa. The opportunity to provide ARV led to the development of Aspen, the largest producer of tablets and capsules in Africa, providing 60% of ARV in South Africa. Following the dispute between global pharmaceutical companies (Pharmaceutical Manufacturers' Association of South Africa filed on behalf of 39 drug companies) and the South African government and the complaint to the Competition Tribunal lodged by Treatment Action Campaign (TAC), domestic manufacturers secured voluntary licences from a significant number of multinational patent-holders to produce a broad array of ARVs. In the settlement agreements with Boehringer Ingelheim and GlaxoSmithKline (GSK), several existing voluntary licensing agreements with Aspen for ARVs were given extended reach. The licences permitted both the production and the sale of nevirapine, AZT and lamivudine (commonly known as 3TC) within South Africa and for export to 47 countries in Africa for a royalty of no more than 5% of net sales. The use of VLA has continued with GlaxoSmithKline, who signed five voluntary licensing agreements for ARVs in South Africa. For example, Aspen has VLAs with:

- 13 TB and HIV/AIDS drugs: nevirapine, efavirenz, atazanavir, tenofovir, tenofovir+emcitrabine, lamivudine, zidovudine, lamivudine+zidovudine, stavudine, didanosine, saquinavir, capreomycin and cycloserine; and
- 93 percent of Aspen's requests for voluntary licences have been granted

The success of these agreements has led to new competitors including Adcock-Ingram, Sonke Pharmaceuticals and Cipla-Medpro (a joint venture between Cipla Ltd of India and Medpro Pharmaceutica), a South African generic pharmaceutical company. It is again noteworthy that the South African domestic industry depends on India for production of API.

Although initiated from a confrontation between the industry, NGOs and government, the continued success of these agreements appears to demonstrate

that voluntary licences can make a valuable contribution to universal ART programmes for the treatment of HIV/AIDS.

In Thailand there is no domestic generic industry although the Government Pharmaceutical Organisation (GPO), the publicly owned manufacturer, played an important role. GPO began research and development into antiretroviral drugs (zidovudine and didanosine) in 1992. GPO produces six antiretroviral drugs and two fixed-dose combinations in a range of dosages, which are between two (for nevirapine) and 25 (for stavudine). For more recent ARV it has imported Indian generics instead of manufacturing itself.

For first-line medicines, Indian generic producers have been important for all case studies with the exception of Mexico. In most cases, first-line products were not subject to the patent regime in India. This has allowed generic manufacturers to produce products. The non-exploitation of patents in SSA and low-income countries means that these have been exportable to countries such as Botswana and Rwanda. Even first-line products where a patent is potentially enforceable have been produced under voluntary licences. Voluntary licensing has been common in India and South Africa, where the local generic industry has proved able to produce generics meeting the appropriate quality standards and to obtain WHO Prequalification certifying it.

Although the great majority of ART treatment in low-income countries has been through generics, it should be noted that for some products, originators continue to offer the best value through not-for-profit pricing and facilitating generic entry through voluntary licensing arrangements.

**First-line versus second-line treatments**

Generic entry has been more pervasive in first-line ARV drugs than it has been in ARV drugs that are only used in second-line combinations. There may be a number of reasons that explain this. Many second-line drugs have been developed only recently, as it is shown in Table 12. In most middle-income countries, we expect these second-line drugs to be still under patent and therefore no generic entry could be expected. In low-income countries and in SSA countries, where these patents are typically not asserted or not enforced, there has been little time for generic manufacturers to develop their generic versions of the drugs and launch then into the market.

Even in some middle-income countries, most second-line drugs are not protected by patents. This is for instance the case in India. Out of 23 ARV drugs that had obtained market authorisation in India in 2008, only two were considered eligible for patent protection because the TRIPS provision on product patents is applicable in India only for drugs developed before January 1995.[202] This pattern applies both to first- and second-line products. As illustrated in Table 12, only two protease inhibitors have been granted patent protection in India, while the rest can be produced by Indian generic manufacturers without the need of a licence agreement and without infringing national patent law. Newer second-line classes of drugs like fusion and entry inhibitors and integrase inhibitors have been granted patent protection in India.

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**202** http://infochangeindia.org/agenda/HIV/AIDS-big-questions/why-are-aids-drugs-unaffordable-in-india.html

Table 12: *Patent status on second generation products in India*

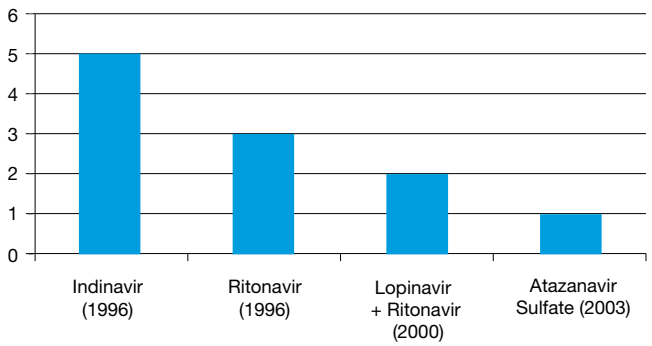
SOURCE: MEDICINES PATENT POOL

| | Product | Year of FDA approval | Patent status in India | Notes |
|---|---|---|---|---|
| Protease inhibitors | Saquinavir (SQV) | 1995 | ~ | The patent on the API has expired. Patents have been granted for an improved composition and an oral dosage form. |
| | Indinavir (IDV) | 1996 | No | No patent on the API. |
| | Ritonavir (RTV) | 1996 | No | No patent exists on the API. The patent for the crystalline polymorph was opposed in 2007. |
| | Nelfinavir (NFV) | 1997 | No | |
| | Amprenavir | 1999 | Yes | |
| | Lopinavir (LPV) + Ritonavir (RTV) | 2000 | ~ | The patent on soft-gel caps was withdrawn. One patent on the Tablet formulation was rejected but divisional applications are pending. A second patent on the Tablet formulation exists, filed in 2007. |
| | Atazanavir (ATV) | 2003 | ~ | The patent on the API was withdrawn, but divisional applications are still pending. The process patent was rejected following pre-grant opposition. |
| | Fosamprenavir (FPV) | 2003 | Yes | Existing patent, filed in 1998. |
| | Darunavir (DRV) | 2006 | ~ | No patent on the API. The combination with RTV was rejected but divisional application is still pending. The combination with RTV and TDF was withdrawn after opposition. The pseudopolymorph and the prep of key intermediates patents were both rejected following pre-grant opposition. |
| Fusion and entry inhibitors | Enfuvirtide (T20) | 2003 | Unknown | |
| | Maraviroc (MVC) | 2007 | Yes | Two patents exist, one for the API, and the other for the crystal form. |
| Integrase inhibitor | Raltegravir (RAL) | 2007 | Yes | Patent granted. |

At present, Indian companies manufacture most drugs that are on the international market for first-line and second-line treatment. Indian companies produce generic versions of all types of protease inhibitors (PIs) used for second-line treatment including the heat stable RTV-boosted lopinavir (LPV/r). However, it is still the case that there are relatively few generics competitors for these products. Figure 47 shows the number of generic manufacturers producing four protease inhibitor drugs that are not patent protected currently in India. Comparing these numbers with those for first-line drugs in Figure 45, we observe that a lower number of generic manufacturers produce protease inhibitors.

Figure 47: *Number of generics for second-line ARV drugs*

SOURCE: WHO DRUG REGULATORY STATUS DATABASE; CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES, «UNTANGLING THE WEB OF ANTIRETROVIRAL PRICE REDUCTIONS,» 2010.




We also observe that the number of generics tends to be higher for the older protease inhibitors than for the newer ones. This suggests that generic entry takes place gradually over a number of years and may partially explain why the most recently developed second-line treatments still face limited generic competition. Demand for second-line treatments is significantly lower than for first-line treatments. Given the relation between market size and number of generics illustrated in Figure 46, we should expect less generic entry in second-line markets than in first-line markets. This may to some extent explain the low generic market shares observed for indinavir and lopinavir+ritonavir (relative to those observed for first-line drugs), even after a substantial number of years.

The production by Indian generic companies reflect the continued lack of patent protection and the existence of voluntary licences — for atazanavir and tenofovir for example.

Most countries reported purchases of innovator PIs whereas far fewer countries reported generic PI purchases, most likely due to lower prices offered through tiered pricing schemes for brand lopinavir/ritonavir in 2003-2008.

**Voluntary licence agreements**

The number of voluntary licence agreements is increasing. Voluntary licences have been agreed in India, Brazil and South Africa. Looking at the experience of our case studies, VLAs for second-line products include:[203]

- Gilead has partnered with Aspen Pharmacare, South Africa to manufacture and distribute branded and generic versions of tenofovir and tenofovir+emticitrabine in Africa. Gilead has entered into non-exclusive licensing agreements with 13 Indian generic companies, allowing them to distribute generic versions of tenofovir and tenofovir-based regimens in 95 developing countries, including India, South Africa and Thailand. The agreements include technology transfer. Most recently Gilead announced new licensing terms with four India-based drug manufacturers for three drugs which are currently in late-stage clinical development.

**203** http://www.future-science-group.com/_img/pics/For-profit_policies_and_equitable_access_to_antiretroviral_drugs_in_resource-limited_countries.pdf

- Merck & Co. has granted royalty-free licences of its ARV efavirenz to five generic manufacturers, of which four are currently on the market.

- ViiV Healthcare participates in eleven royalty-free voluntary licence agreements to generic manufacturers, mainly Indian manufacturers, covering its portfolio.

VLAs exist also for second-line treatments:

- BMS licensed atazanavir in SSA and in India to Aspen and Emcure in February 2006.

- Tibotec licensed darunavir to Aspen in SSA in April 2007. In January 2011, Tibotec signed voluntary licence agreements with Hetero Drugs Ltd., Matrix Laboratories Ltd. (Mylan) and Aspen Pharmacare which include technology transfer. The agreements require the generic manufacturers to pay royalties ranging from 2 to 5%. Hetero Drugs and Matrix will be able to market the drug in SSA, LDCs and India, while Aspen will only be able to market the product in SSA, including South Africa.[204]

- Roche licensed companies in Ethiopia and Zimbabwe to produce saquinavir for SSA in May 2007.

However, we have not been able to identify the relative importance of manufacturers using these licences (this would be a useful addition to the GPRM dataset).

The impact of these new competitors on the market for new medicines will take time to observe (as it did for first-line products). For example, Gilead's voluntary licence to Matrix for tenofovir in Thailand is expected to have a significant impact on prices going forward (even after allowing for the tier pricing Gilead already has in place).

However, generic competition is already having an impact. In the recent announcement by CHAI and DiFID, the price of the most affordable generic second-line drug regimen — TDF, 3TC and LPV/r — was reduced to $170 annually, a 16% decrease from the 2008 level, and 18% and 39% lower than the average market prices in low- and middle-income countries respectively. As part of these negotiations, agreements with three generic suppliers were announced for the supply of heat-stable LPV/r at a price of $470 per patient per year, and the introduction of generic versions of atazanavir (ATV) and heat-stable ritonavir (RTV).[205]

Although, second-line medicines do have IP protection in middle-income markets, this does not seem to be the fundamental reason for high prices. These products are already being produced by Indian generics companies (sometimes under licence) and their prices remain significantly above first-line therapies. This suggests that prices reflect the smaller size of the second-line market and the more complex manufacturing processes, rather than IP protection.

In conclusion, the emergence of generic sources supplying quality ARV medicines at prices lower than originator prices have contributed to accelerate the scale-up of HIV/AIDS treatment in the case study countries.

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**204** http://www.jnj.com/connect/news/all/tibotec-signs-multiple-agreements-with-generic-manufacturers-to-provide-access-to-new-hiv-treatment

**205** http://www.ihs.com/products/global-insight/industry-economic-report.aspx?ID=1065929722. The reduced prices will be available to over 70 developing countries that are members of the CHAI Procurement Consortium in Africa, Asia, Eastern Europe, Latin America, and the Caribbean, and will also be extended to Global Fund to Fight AIDS, Malaria and Tuberculosis (the Global Fund) recipients participating in that body's new Voluntary Pooled Procurement scheme.

SSA countries with high HIV/AIDS burdens, as well as India, are heavily reliant on the availability of Indian-produced generic ARVs to support their national treatment programmes.

Local production of non-patented first-line drugs, coupled with price negotiations with pharmaceutical companies for newer drugs subject to patent, has helped governments to steadily reduce their average annual cost for ART.

### 4.5.7 Compulsory licensing

The case studies suggest that the use of compulsory licensing or provision of generics through using Paragraph 6 have not played a significant part in improving access. Very few products have been compulsory licensed (and even less have used Paragraph 6 provisions).

In a limited number of cases, national governments have chosen to respond by issuing compulsory licences allowing local generic companies to produce generic versions of patented ARV drugs. Brazil issued a compulsory licence for efavirenz in 2007 after unsuccessful negotiations with the branded manufacturer, Merck & Co. Thailand issued compulsory licences for efavirenz and lopinavir/ritonavir (Abbott) in the same period. However, given the number of possible products and countries involved, the use of compulsory licensing remains very limited.

The Doha Declaration includes a waiver of the TRIPS Agreement to allow the issuance of compulsory licences in countries where patents are valid to be exported to countries that lack production capacity, the so-called Paragraph 6 provision. Interestingly, Rwanda has been the only country to import generics using Paragraph 6 of the Doha declaration. In July 2007 Rwanda decided to import a limited amount of a generic fixed-dose combination of zidovudine, lamivudine and nevirapine from a Canadian generic manufacturing company. To make it possible, Canadian authorities issued a compulsory licence in favour of the generic producer Apotex.[206]

While there have been few cases of compulsory licensing, the threat of issuing a compulsory licence may have been useful for national governments in the price negotiations with pharmaceutical companies — indeed, it has been suggested that the threat of compulsory licensing has been successfully used in a number of cases to obtain significant discounts from branded manufacturers.[207] We look at this in more detail in the following chapter. However, it is also the case that countries that have not used compulsory licensing have also achieved substantial cost savings through negotiation.

### 4.5.8 The role of public-private partnerships

Public-private partnerships have had a role in all the countries in our case studies, although their contribution to the current access to ART varies substantially. The objectives of public-private partnerships vary from country to country. Partnerships have often included donations and preferential supply of ARVs in low-income and SSA countries (Botswana, Rwanda, South Africa), as well as capacity building. In middle-income countries (Brazil, India, Mexico, Thailand) partnerships have tended to focus primarily on capacity building. Partnerships

**206** UNAIDS (2010), "Using TRIPS flexibilities to improve access to HIV treatment".
**207** Beall and Kuhn (2010), "Trends in International Compulsory Licensing for Pharmaceutical", Mimeo.

involving technology transfer have been relevant especially in India and South Africa, where originators and local generic manufacturers cooperate through voluntary licences.[208]

Botswana clearly stands out as one of the most successful experiences of a public-private partnership that has made a difference by raising access to ART. Close collaboration between the government of Botswana, the Gates Foundation and Merck & Co. / the Merck Company Foundation has proved a unique experience in terms of developing a comprehensive strategy balancing capacity building and ARV supply at a large scale. Precisely due to the magnitude of the effort that ACHAP has required from all the partners, it is not seen as replicable elsewhere. There are however valuable lessons to be learned from it, not least that increasing access to ART requires commitment, resources and balancing a number of complementary interventions.

## 4.6 CONCLUSIONS

Drawing on the experience of the case studies, there are a number of clear themes that emerge regarding the effectiveness of interventions. Firstly, the date when the universal ARV programmes were initiated is clearly important and this reflects political will and commitment. It is hardly surprising that programmes starting earlier — in Brazil and Botswana — have been the most successful in achieving high levels of access to ARVs, while the countries with programmes that were not initiated until later have been forced to play catch-up throughout the last decade. In many cases, the countries not initiating their ARV programmes until later initially focused on prevention activities and were more sceptical about the effectiveness of ART. In these countries, coverage rates have risen more slowly and have still not caught up with countries that focused on ART coverage in earlier years.

The speed at which it has been possible to improve access depends on development in the domestic health infrastructure and associated programmes to address stigma. Building up necessary infrastructure takes time and it is one of the primary reasons that countries struggle to raise access levels at an accelerated rate, being instead forced to raise access more gradually over time.

There is however little doubt that by improving education and reducing stigma, countries can reduce major barriers that exist for patients seeking out voluntary testing and treatment, which is critical for reducing the time to diagnosis and initiating effective treatment regimens.

The substantial increase in resources from the international community that has been dedicated to promoting health over the last several years has begun to change the trajectory of the HIV/AIDS epidemic in the poorest countries, as evidenced by the case studies of Rwanda, Botswana and South Africa. Only once the Global Fund, PEPFAR, the Gates Foundation and UNAIDS focused resources did access start to improve for the poorest countries. Middle-income countries have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit.

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**208** IFPMA Partnerships Directory (http://www.ifpma.org/resources/partnerships-directory.html)

The innovative industry has contributed to the affordability of ARVs through differential pricing, which emerged as a common practice at the beginning of the decade. This has benefited all of the case studies examined. Each country has its own position regarding their access to differential pricing schemes depending on their income level and the state of their epidemic. Rwanda is a low-income country with a high degree of prevalence, so it has access to the lowest prices. Botswana and South Africa also generally have access to the lowest prices because they are SSA countries with large epidemics. Brazil, Mexico and Thailand are middle-income countries with concentrated epidemics; hence they do not usually have access to the same pricing arrangements as the countries named above. However, they are still usually offered discounted pricing.

Generic manufacturers have been important in all of the case studies, with the exception of Mexico. However, this varies significantly from country to country. In Brazil, Thailand, India and South Africa, domestic suppliers have played an important role for first-line ARTs. In Botswana and Rwanda, Indian generics have played an important role through pooled and direct purchases. This is clearly the case for first-line treatments and will play a similar role of second-line treatments in the future. Voluntary licence agreements have played a significant role in the development of generics, particularly in South Africa and are increasingly important to Indian generics provision of second-line medicines.

The case studies suggest that the use of compulsory licensing or provision of generics through using Paragraph 6 have not directly played a significant part in improving access. Very few products have been compulsory licensed (and even less have used Paragraph 6 provisions).

In conclusion, the key factors explaining access in the case studies varies from country to country. The conclusions from the case studies in terms of whether factors were significant in raising access to the current level are set out in Table 13.

Table 13: *Overview of key factors responsible for increasing access in the case studies*

SOURCE: CRA ANALYSIS

| | Rwanda | India | Thailand | Brazil | Botswana | Mexico | South Africa |
|---|---|---|---|---|---|---|---|
| Political will | *** | * | *** | *** | *** | *** | ** |
| Overcoming stigma | ** | * | Unknown | *** | ** | Unknown | ** |
| Domestic healthcare capacity | ** | * | ** | ** | *** | *** | ** |
| International funding | *** | ** | * | * | ** | * | ** |
| Negotiation and procurement | *** | * | * | * | * | ** | *** |
| Generic manufacturers | *** | *** | *** | *** | ** | * | *** |
| Compulsory licensing | * | N/A | * | * | N/A | N/A | N/A |
| Partnerships | *** | ** | ** | * | *** | * | ** |

*** represent a significant factor in raising access to the current level
* represent a minor factor in raising access to the current level

# 5

# A STATISTICAL ANALYSIS OF THE DETERMINANTS OF ACCESS TO ART

As illustrated by the case studies, the approaches to expanding access to ART that have been taken in different countries have varied significantly. Changes in political commitment, funding for medicine purchases, investment in healthcare capacity and ARV prices often coincide. In order to try to identify the relative importance of each factor we have undertaken two types of analysis, focusing on:

- The factors determining access to ART across countries and over time; and
- The factors determining the price of common ART across countries and over time.

## 5.1 DATA UNDERLYING THE ANALYSIS

The objective of the analysis is to test whether there is correlation between measures of access and variables that act as proxies for different policy interventions identified in Chapter 3.

To conduct the statistical analysis we have combined data from different sources. Data on ART coverage rates has been obtained from the WHO. Data on expenditures in HIV programmes comes from UNAIDS. Other country characteristics have been obtained from the World Bank, including per capita income, HIV prevalence and health expenditures, among others. Data on price and market structure has been obtained from the WHO Global Price Reporting Mechanism (GPRM). Table 14 reports the variables used and their data sources.

Table 14: *Description of variables and data sources*

SOURCE: CRA

| | Variable | Description | Source |
|---|---|---|---|
| Access measure | ART coverage rate (2006 guidelines) | Share of HIV-positive patients needing ART that actually receive it in a country. Annual observations. | WHO |
| Country character-istics | Log of per capita income | Measure of the country's wealth. Annual observations in nominal US$. | World Bank |
| | Gini index | Measure of the degree of inequality in the distribution of income within a country. Takes values between 0 and 1. A lower value indicates a more equal distribution of income across households. No time variation, average value for the period 2000-2009. | CRA based on World Bank |
| | HIV prevalence rate | Share of population in a country that is HIV positive. Annual observations. | World Bank |
| | Sub-Saharan Africa | Binomial variable taking value 1 if a country is in sub-Saharan Africa, 0 otherwise. No time variation. | CRA |
| Policy interventions | Starting year of ART programs | Year when large-scale programs for HIV treatment were first launched in a country. The variable suffers from left-hand censorship, with all countries that initiated treatment programs in the 90s taking value 2000. No time variation. | WHO |
| | Health expenditure as % of GDP | Share of national income spent in healthcare in a country, both public and private resources. Annual observations. | World Bank |
| | HIV expenditure as % of GDP | Share of national income spent in HIV-related healthcare services in a country, including prevention, testing, treatment, etc. Annual observations. | UNAIDS |
| | Foreign HIV aid as % of HIV expenditure | Share of expenditure in HIV-related healthcare services funded from foreign sources. Annual observations. | UNAIDS |
| | Compulsory licensing | Binomial variable taking value of 1 after the country has used compulsory licensing, 0 otherwise. | CRA |
| Prices and market structure | Average annual cost of treatment | Average cost of providing the quantities needed to cover one-year of treatment with a single ARV drug in a country. It does not represent the total annual cost of ART, as this typically consists of a combination of at least three ARV drugs. Annual observations in nominal US$. | CRA based on WHO GPRM |
| | Branded annual cost of treatment | Cost of providing the quantities needed to cover one-year of treatment with a branded version of a single ARV drug in a country. Annual observations in nominal US$. | CRA based on WHO GPRM |
| | Generic annual cost of treatment | Cost of providing the quantities needed to cover one-year of treatment with a generic version of a single ARV drug in a country. Annual observations in nominal US$. | CRA based on WHO GPRM |
| | Number of generics supplying the country | Number of generic manufacturers that have simultaneously supplied an ARV drug in a country in a given year. Annual observations. | CRA based on WHO GPRM |

The variables set out in Table 14 are intended to proxy for the policy interventions discussion in chapters 3 and 4. However, we have not been able to find a variable that appropriately captures each of the effects. For example, the year when the ART programme starts could be used as a measure of political will but is clearly imperfect. The compulsory licence variable captures when this has been used. This variable could also be capturing the effect that the perceived threat of compulsory licensing may have, but only to the extent that countries that have actually used compulsory licensing are perceived as being more likely to use it again.

Data describing the country characteristics and policy interventions highlighted above has been gathered. The resulting dataset contains yearly data at the country level for a number of low- and middle-income countries over the period 2004-2009. The dataset includes data from 76 low- and middle-income countries in 2008, the year for which the lowest number of countries is observed, and 79 countries in 2004 and 2006, the years when the most countries are observed. Although for some variables not all countries have observations for the entire period, this dataset provides a comprehensive picture of these dimensions in low- and middle-income countries during the last decade.

Table 15: *Provides summary statistics for the variables containing information on country characteristics and policy interventions.*

SOURCE: CRA

| Variable | Number of Observations | Mean | Standard Deviation | Minimum value | Maximum value |
|---|---|---|---|---|---|
| ART coverage rate (2006 guidelines) | 466 | 33.42 | 26.55 | 0.00 | 95.00 |
| Log of per capita income | 466 | 7.17 | 1.11 | 4.53 | 9.33 |
| Gini index | 466 | 0.43 | 8.21 | 28.00 | 59.50 |
| HIV prevalence rate | 466 | 2.59 | 4.85 | 0.10 | 25.90 |
| Sub-Saharan Africa | 466 | 0.41 | 0.49 | 0.00 | 1.00 |
| Starting year of ART programs | 466 | 2003 | 2.40 | 1999 | 2007 |
| Health expenditure as % of GDP | 466 | 0.06 | 0.02 | 0.02 | 0.15 |
| HIV expenditure as % of GDP | 220 | 0.0042 | 0.0074 | 0.000034 | 0.051 |
| Foreign HIV aid as % of HIV expenditure | 210 | 0.62 | 0.32 | 0.01 | 1.00 |

A second dataset has been created with data on prices of ARV drugs obtained from the WHO GPRM. The GPRM contains information on transaction prices and quantities of ARV medicines purchased by HIV/AIDS Programmes in low- and middle-income countries. Currently, the GPRM includes prices of ARV drugs purchased and supplied by various procuring agencies for different countries.[209] The GPRM primarily contains information about national procurements made with external donor funding and does not typically contain information about procurements from countries that are self-funding HIV/AIDS treatment. This dataset has also been used by Waning, Kyle et al. (2010) and Waning, Kaplan et al. (2010) to investigate the trends in prices of ARV drugs in low- and middle-income countries over the period 2002-2009.[210]

**209** Available from http://www.who.int/hiv/amds/gprm/en/.
**210** Recently, they have used this dataset to undertake an econometric investigation into whether price depends on the purchasing channel. This looked at whether the price varied depending on whether differential pricing of branded medicines was used or purchases were made through pooled procurement vehicles such as CHAI. http://www.who.int/bulletin/volumes/87/7/08-058925/en/

We have used the data on transaction prices from the GPRM to produce average prices per country and year for a selection of ARV medicines. The resulting dataset contains information on prices for the period 2003-2009 in a limited number of countries. Table 16 reports the ARV drugs for which information on prices has been collected.

Table 16: *ARV drugs included in the dataset with price data*

SOURCE: CRA

| Active principle | Number of countries | Period |
|---|---|---|
| Didanosine (ddI) | 86 | 2003-2009 |
| Efavirenz (EFV) | 105 | 2003-2009 |
| Lamivudine (3TC) | 93 | 2003-2009 |
| Lopinavir + Ritonavir (LPV/r) | 101 | 2003-2009 |
| Nevirapine (NVP) | 98 | 2003-2009 |
| Stavudine (d4T) | 87 | 2003-2009 |
| Tenofovir (TDF) | 74 | 2004-2009 |
| Zidovudine (AZT) | 83 | 2003-2009 |

Table 17 shows the number of low- and middle-income countries for which yearly pricing information is available for at least some of the selected ARV medicines.[211]

Table 17: *Number of low- and middle-income countries with price data*

SOURCE: CRA

| Year | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 |
|---|---|---|---|---|---|---|---|
| Low-income countries | 6 | 33 | 40 | 43 | 41 | 29 | 29 |
| Lower middle-income countries | 2 | 17 | 29 | 27 | 29 | 35 | 31 |
| Upper middle-income countries | 1 | 8 | 8 | 10 | 14 | 19 | 9 |
| All low- and middle-income countries | 9 | 58 | 77 | 80 | 84 | 83 | 69 |

**211** Clearly there is a concern that the data underlying the GPRM is not representative of the purchases of HIV medicines in particular countries. However, it is clear that it does cover purchases made in a wide range of markets. For the case study countries, we have augmented the data set using existing reports of public prices for these countries.

Parts of the statistical analysis that use data on prices are based on the sub-sample of countries covered by both datasets.

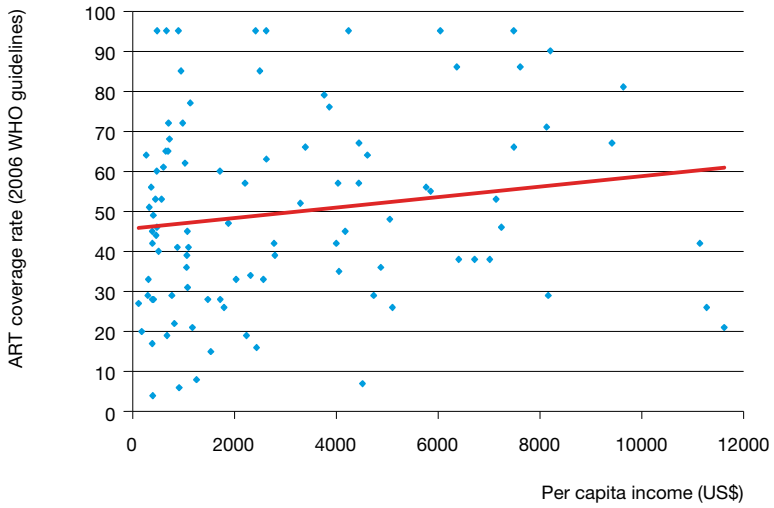
## 5.2 A STATISTICAL ANALYSIS OF FACTORS AFFECTING ART COVERAGE IN LOW- AND MIDDLE-INCOME COUNTRIES

This analysis looks at whether there is a correlation between access (as measured by the 2006 WHO definition) and factors such as: the year when the universal access programme was initiated, average income, region, distribution of income, amount spent on HIV, average price of common ARVs and use of IP policy tools (ex. compulsory licensing). This approach is similar to the analysis conducted by Peiffer and Boussalis (2010). We have developed their methodology to include a range of other explanatory factors.[212]

As described in Chapter 2, ART coverage rates have increased globally during the period 2004-2009 but the degree of dispersion in levels of coverage has diminished considerably and countries with lower income seem to have been able to approach levels of coverage of countries with relatively higher levels of income. The level of income continues to be positively correlated with ART coverage rates, as shown in Figure 48. The trend line in the figure shows this positive correlation in 2009. The scatter plot shows as well that the dispersion in the levels of ART coverage is substantially higher for countries at the bottom end of the income distribution. Countries with similar level of per capita income present very different rates of ART coverage.

Figure 48: *ART coverage rates versus per capita income in 2009 in low- and middle- income countries*

SOURCE: CRA




**212** The model developed by Peiffer and Boussalis (2010) used a similar data set covering between 58 and 72 countries in a cross-section analysis. Their models included a range of factors. Most are shared by our analysis, including income, prevalence, HIV expenditure and sub-Saharan dummy. However, they also included a number of variables we have not included, like urbanisation, female labour and democracy. However, these factors are not included in their base model, just in the extended models. Our Gini variable may capture a similar characteristic as their urbanisation variable, e.g. population polarisation in different socioeconomic categories. They do not find female labour and democracy to be significant and we do not have any additional reason to include them in our specifications.

To identify what factors other than income are associated with higher levels of access to ART, like characteristics of the countries and policy interventions, we have used the following two specifications of a linear regression model:

$$ARTcoverage_{it} = \alpha + characteristics_{it}'\beta_1 + interventions_{it}'\delta + timecontrols_{it}'\gamma + \varepsilon_{it}$$
$$ARTcoverage_{it} = \alpha + characteristics_{it}'\beta_1 + interventions_{it}'\delta + \gamma\, drugcost_{it} + \varepsilon_{it}$$

Where

- *ARTcoverage* is the ART coverage rate according to the 2006 WHO guidelines in a given country *i* at year *t*;
- *Characteristics* is a vector of country characteristics including per capita income, the Gini index of income distribution within the country, the HIV prevalence rate and whether the country is in the sub-Saharan region;
- *Interventions* is a vector including the year in which large-scale ART programmes where first launched in the country, the total expenditure in HIV programmes as a share of the national income and whether compulsory licensing has ever been used in the country;
- *Timecontrols* is a vector of dummy variables (taking the value of 1 for observations in the appropriate year) introducing year-fixed effects into the regression; and
- *Drugcost* is a variable capturing the annual cost of drug treatment in low-, lower middle- and upper-middle-income countries each year.

We have estimated the coefficients in this model by ordinary least squares (OLS) and the resulting estimates are reported in Table 18.[213]

**213** As in Peiffer and Boussalis (2010) we have also estimated the regression using generalised least squares with a binomial distribution to allow for coverage being bounded between 0 and 1. The results of this are consistent with the OLS regressions.

Table 18: *Estimates from regressions of ART coverage rates*

SOURCE: CRA;

| Explained variable: ART coverage rate | All countries (1) | All countries (2) | All countries (3) | Low income | Lower middle-income | Upper middle-income |
|---|---|---|---|---|---|---|
| Log of per capita income | 0.029** (0.012) | 0.052*** (0.000) | 0.110*** (0.000) | -4.5E-04 (0.988) | 0.125*** (0.004) | 0.052 (0.544) |
| Gini index | 0.003*** (0.004) | 0.003*** (0.004) | 0.002 (0.335) | 0.002 (0.248) | 0.004** (0.017) | 0.004 (0.134) |
| HIV prevalence rate | 0.007*** (0.004) | 0.006*** (0.009) | -0.005 (0.279) | 0.009*** (0.001) | 0.006 (0.169) | -0.022* (0.073) |
| Sub-Saharan Africa | -0.128*** (0.000) | -0.120*** (0.000) | -0.106** (0.013) | -0.149** (0.000) | -0.064 (0.282) | 0.135 (0.336) |
| Starting year of ART programs | -0.047*** (0.000) | -0.046*** (0.000) | -0.044*** (0.000) | -0.057*** (0.000) | -0.027*** (0.001) | -0.036** (0.012) |
| Health expenditure as share of GDP | 0.015*** (0.001) | 0.017*** (0.000) | | 0.004 (0.486) | 0.032*** (0.001) | 0.048*** (0.007) |
| HIV expenditure as share of GDP | | | 12.287*** (0.000) | | | |
| Foreign HIV aid as share of HIV expenditure | | | 0.132* (0.077) | | | |
| Use of compulsory licensing | 0.059 (0.469) | 0.057 (0.492) | 0.120 (0.199) | no obs. | 0.154 (0.287) | 0.082 (0.508) |
| Annual cost of treatment with efavirenz | | -0.001*** (0.000) | -0.001*** (0.000) | -0.001*** (0.000) | -0.001*** (0.000) | -1.6E-04 (0.350) |
| Dummy year 2005 | 0.051 (0.100) | | | | | |
| Dummy year 2006 | 0.120*** (0.000) | | | | | |
| Dummy year 2007 | 0.170*** (0.000) | | | | | |
| Dummy year 2008 | 0.235*** (0.000) | | | | | |
| Dummy year 2009 | 0.295*** (0.000) | | | | | |
| Constant | 94.863*** (0.000) | 91.642*** (0.000) | 88.329*** (0.000) | 114.482*** (0.000) | 52.582*** (0.001) | 71.021*** (0.013) |
| Number of observations | 472 | 472 | 213 | 213 | 160 | 99 |
| R squared | 0.4989 | 0.4822 | 0.4282 | 0.5948 | 0.3689 | 0.3283 |

( ) REPRESENTS THE SIGNIFICANCE LEVEL.
*** IS USED TO DENOTE SIGNIFICANCE AT 1%
** AT 5%
* AT 10%

The first three columns of results in Table 18 report the coefficients for three different specifications estimated pooling all countries. In each we report the coefficients from the regression analysis, the number of observations used in the analysis and the R-squared (a measure of how well the model fits the data).[214]

The first specification includes time dummies to capture any time trend in the evolution of ART coverage over time. The second specification includes the annual cost of treatment with a large first-line medicine (efavirenz) instead of time dummies. Inclusion of both the cost variable and the time dummies in the same specification causes multicollinearity due to the highly negative correlation between time and prices, which have decreased steadily during the period. Table 19 shows correlations between the annual cost of treatment with a number of different ARV drugs and time. It is clearly the case that average prices fall over time, an aspect that we investigate with greater detail in the next section. It is also the case that there is a clear and positive time trend, as shown by the reported estimates.

Table 19: *Partial correlations between time and prices of ARV drugs*

SOURCE: CRA

| | Year | Efavirenz | Indinavir | Lamivudine | Lopinavir/r | Stavudine | Tenofovir | Zidovudine |
|---|---|---|---|---|---|---|---|---|
| **Year** | 1 | | | | | | | |
| **Efavirenz** | -0.6331 | 1 | | | | | | |
| **Indinavir** | -0.1356 | 0.3394 | 1 | | | | | |
| **Lamivudine** | -0.1770 | 0.3967 | 0.1200 | 1 | | | | |
| **Lopinavir/r** | -0.3168 | 0.4721 | 0.3787 | 0.2314 | 1 | | | |
| **Stavudine** | -0.2142 | 0.7692 | 0.2378 | 0.3421 | 0.4069 | 1 | | |
| **Tenofovir** | -0.2813 | 0.6864 | 0.2597 | 0.2707 | 0.7302 | 0.7812 | 1 | |
| **Zidovudine** | -0.4940 | 0.5423 | 0.1110 | 0.1338 | 0.1128 | 0.3033 | 0.2878 | 1 |

**214** For a model of this kind that includes a wide cross-section of different countries an R-squared of 0.4-0.5 would be seen as satisfactory.

To select the annual cost of treatment with efavirenz as our indicator for ARV prices, we have initially included the cost of all ARV drugs in a single specification. We have iteratively run the regression, successively dropping the ARV drug with the lowest statistical significance. This process has led us to the selection of the annual cost of efavirenz, which captures almost the whole effect associated with the time trend. While this is our best measure of the effect of the decline in ARV prices on ART coverage, this variable may at the same time be capturing other factors correlated with prices and that have contributed to increase access to ART.[215]

The specification in the third column uses expenditure in HIV programmes instead of health expenditure and distinguishes between domestic expenditure and foreign aid for HIV. However, this comes at the cost of losing a substantial number of observations, as data on HIV expenditure is only available for a limited amount of countries and years.

The estimates from these specifications show that the level of access increases depending on a number of factors. In particular, the level of access is positively correlated with:

- Per capita income in the country;
- The inequality in the distribution of income within the country;
- The prevalence rate;
- The country being outside of the SSA region;
- The time since large-scale ART programmes were started;
- The expenditure on prevention, treatment and management of HIV in total;
- The weight of foreign aid in HIV programmes; and
- The lower cost of ARV treatment.

Additionally, the specification in the second column has been estimated separately for low-, lower middle- and upper middle-income countries; to investigate whether these factors have different importance depending on the group of countries. Estimates are reported in the fourth, fifth and sixth columns of results, respectively:

- Income per capita and income distribution are only significant for lower middle-income countries;
- HIV prevalence is positively correlated and significant only for low-income countries;
- Total health expenditure is not significant for low-income countries; and
- The cost of ARV drugs is not correlated with ART coverage for upper middle-income countries.

**215** Another approach would have been to construct an index of annual costs for a variety of medicines. Given the relatively high correlation between the product, this is unlikely to change the overall analysis but is a potentially useful area for future research.

### 5.2.1 Interpretation of the results

These results are overall consistent with our expectations about the relation between ART coverage and the investigated factors. It is unsurprising that overall, higher income countries (per capita income) have higher levels of access as richer countries are likely to face less financial constraints in providing healthcare services to their populations. However, this is true in particular for lower middle-income countries. When restricting the sample to low-income countries, this correlation becomes insignificant. This is consistent with the fact that HIV programmes in low-income countries are mainly funded through foreign aid, with poorer countries typically receiving more external funds, allowing them to get higher access than they could afford with just domestic resources. Income per capita is also insignificant for upper middle-income countries, suggesting that their level of ART coverage is not constrained by the lack of domestic resources.

The fact that HIV prevalence is positively correlated with higher ART coverage is consistent with a bigger effort being made to guarantee access to ARV drugs in those countries where the HIV epidemic is of largest concern. The positive correlation is only significant for low-income countries, which is consistent with foreign aid being directed towards low-income countries facing the toughest epidemics. In upper middle-income countries prevalence is significant and negatively correlated with ART coverage, which is consistent with higher prevalence posing a harder challenge to countries that do not receive international aid.

After controlling for level of income per capita, income distribution and level of prevalence, SSA countries show lower ART coverage. This might be surprising given the international attention focused on SSA but could be explained by demographic factors like ethnic diversity and size of rural population or institutional factors like political instability and conflict.

Large-scale treatment programmes require developing appropriate healthcare infrastructure and capacity, which takes time. It is therefore unsurprising that countries that started their programmes earlier are at a more advanced stage in the provision of ART to their patient population. Moreover, countries that launched their programmes earlier are likely to be those where political will to fight the HIV/AIDS epidemic has been more vigorous, which is also consistent with a negative correlation.

We also expected higher expenditure in healthcare in general and in HIV programmes in particular to reduce barriers to ART, as we find in the statistical analysis. As more resources are being invested in fighting HIV locally, then higher shares of patient population are reached. However, interestingly, total health expenditure is not significant for low-income countries. This is likely to be related to the fact that HIV expenditure in some of these countries has been high in spite of lacking a strong health system and having low levels of general healthcare provision. In such a case, total health expenditure underestimates the importance of HIV in the country and fails to identify a significant effect that may still be present. In fact, foreign spending is mainly directed toward low-income countries and is shown to be significant and positively correlated with access to ART.

Finally, we find that the cost of ARV drugs is negatively correlated with ART coverage and statistically significant, but that compulsory licensing is not significant. The price effect is particularly important for low- and lower middle-income countries, which are the most likely to face financial constraints. We do

not observe any correlation between the cost of ARV drugs and ART coverage in upper-middle-income countries, suggesting that prices of ARV drugs do not constrain access to ART in these countries.

We do not find the level of ART coverage to be correlated with the use of compulsory licensing in Brazil and Thailand. Once we have controlled for all the factors above, Brazil and Thailand do not show higher levels of access than other countries since the issuing of compulsory licences.[216]

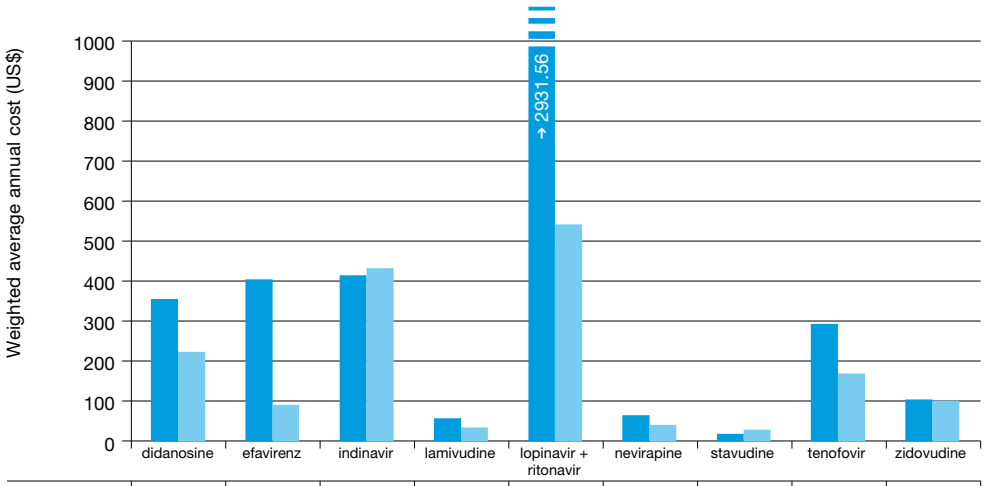
## 5.3 A STATISTICAL ANALYSIS OF FACTORS AFFECTING ARV PRICES IN LOW- AND MIDDLE-INCOME COUNTRIES

A similar analysis has been undertaken to understand the factors that determine the price of ARV medicines. In this case we undertook a statistical analysis for a range of first-line medicines, incorporating into the analysis the data from the WHO GPRM. For each product we looked at whether the price depends on a number of characteristics of the market.

Data for a selection of common ARV drugs show a downward trend for prices over the last decade. Figure 49 shows the change on absolute average annual cost in low- and middle-income countries between 2003 and 2009.

Figure 49: *Annual cost of treatment in 2003 and 2009 for a selection of ARV drugs*

SOURCE: CRA




| | didanosine | efavirenz | indinavir | lamivudine | lopinavir + ritonavir | nevirapine | stavudine | tenofovir | zidovudine |
|---|---|---|---|---|---|---|---|---|---|
| 2003 | 356.09 | 404.88 | 415.04 | 58.17 | 2931.56 | 65.77 | 19.24 | 293.19 | 105.35 |
| 2009 | 224.00 | 91.50 | 432.69 | 34.75 | 542.56 | 41.20 | 29.43 | 170.08 | 101.59 |

216 However, as only Brazil and Thailand have used compulsory licences we need to be cautious in the interpretation of this result.

To capture the effects of country and market characteristics on prices and the downward time trend, we have used the following linear regression model:

$$annualcost_{it} = \alpha + \beta_1 income_{it} + \beta_2 subsaharan_{it} + \beta_3 compulsory\ lic_{it} + \beta_4 generics_{it} +$$

Where

- *Annualcost* is the cost of one year of treatment in a given country i at year t;
- *Income* is the per capita income;
- *Subsaharan* identifies whether the country is in the sub-Saharan region;
- *Compulsorylic* identifies whether compulsory licensing has ever been used in the country;
- *Generics* gives the number of generics that have supplied the country; and
- *Timecontrols* is a vector of dummies introducing year fixed effects into the regression.

We have estimated this model by ordinary least squares for the following ARV drugs: didanosine, efavirenz, lamivudine, lopinavir+ritonavir, nevirapine, stavudine, tenofovir and zidovudine.

Regressions have been estimated for the average annual cost in the market, the annual cost of the branded product and the average annual cost of generic products. The resulting estimates are reported in Table 20, where each column corresponds to a different ARV drug. Columns are ordered from left to right according to the year of launch of each drug into the market, zidovudine being the oldest and tenofovir the newest.

Table 20: *Estimates from regressions of prices*

SOURCE: CRA

## Average annual cost

| Explained variable: Average annual cost | Zidovudine | Didanosine | Stavudine | Lamivudine | Nevirapine | Efavirenz | Lopinavir + Ritonavir | Tenofovir |
|---|---|---|---|---|---|---|---|---|
| **Log income p.c.** | **0.47** (0.967) | **107.96**$^{***}$ (0.000) | **4.72** (0.476) | **54.40**$^{***}$ (0.000) | **19.87** (0.176) | **35.66**$^{***}$ (0.003) | **266.95**$^{***}$ (0.000) | **145.64**$^{***}$ (0.000) |
| Sub-Saharan Africa | **-240.94**$^{***}$ (0.006) | **-747.04**$^{***}$ (0.000) | **-78.91** (0.140) | **-138.93** (0.237) | **-168.24** (0.127) | **-207.66**$^{**}$ (0.019) | **-5323.92**$^{***}$ (0.000) | **-1191.43**$^{***}$ (0.000) |
| **Compulsory lic.** | **2.80** (0.979) | **-24.90** (0.926) | **-20.73** (0.738) | **-37.02** (0.802) | **-21.76** (0.887) | **-153.40** (0.111) | **-46.44** (0.949) | **-106.88** (0.662) |
| **Number of generics in the country** | **-35.71**$^{***}$ (0.008) | **-139.76**$^{***}$ (0.000) | **-6.99** (0.395) | **-62.92**$^{***}$ (0.000) | **-45.56**$^{***}$ (0.005) | **-46.78**$^{***}$ (0.000) | **108.31** (0.360) | **-28.84**$^{**}$ (0.455) |
| **Year** | **-6.14** (0.499) | **-5.12** (0.794) | **-4.53** (0.442) | **-0.62** (0.961) | **-21.10**$^{*}$ (0.089) | **-49.92**$^{***}$ (0.000) | **-83.05** (0.131) | **-33.88** (0.238) |
| **No Saharan country interacted with year** | **-31.33**$^{**}$ (0.013) | **-79.18**$^{***}$ (0.005) | **-10.49** (0.194) | **-23.65** (0.169) | **-25.51** (0.119) | **-22.22**$^{*}$ (0.085) | **-604.66**$^{***}$ (0.000) | **-153.08**$^{***}$ (0.000) |
| **Constant** | **481.76**$^{***}$ (0.000) | **361.21**$^{*}$ (0.095) | **131.61**$^{*}$ (0.035) | **-34.53** (0.807) | **365.10**$^{***}$ (0.006) | **644.48**$^{***}$ (0.000) | **4696.51**$^{***}$ (0.000) | **712.40**$^{***}$ (0.008) |
| **Observations** | 300 | 301 | 267 | 325 | 371 | 397 | 324 | 194 |
| **R squared** | 0.1141 | 0.2861 | 0.0438 | 0.1261 | 0.1029 | 0.3477 | 0.5468 | 0.3783 |

## Branded annual cost

| Explained variable: **Branded annual cost** | Zidovudine | Didanosine | Stavudine | Lamivudine | Nevirapine | Efavirenz | Lopinavir + Ritonavir | Tenofovir |
|---|---|---|---|---|---|---|---|---|
| Log income p.c. | 1.64<br>(0.898) | 107.64***<br>(0.000) | 5.27<br>(0.503) | 49.33***<br>(0.004) | 19.97<br>(0.283) | 38.49**<br>(0.011) | 225.86***<br>(0.001) | 141.40***<br>(0.000) |
| Sub-Saharan Africa | -260.42***<br>(0.008) | -754.52***<br>(0.000) | -48.98<br>(0.440) | -265.05**<br>(0.043) | -171.54<br>(0.220) | -270.95**<br>(0.016) | -4931.61***<br>(0.000) | -1208.20***<br>(0.000) |
| Compulsory lic. | -16.33<br>(0.889) | -25.33<br>(0.929) | -14.39<br>(0.845) | -472.34***<br>(0.004) | -18.08<br>(0.926) | -91.66<br>(0.451) | -6.40<br>(0.993) | -26.66<br>(0.916) |
| Number of generics in the country | -47.42***<br>(0.002) | -207.02***<br>(0.000) | -8.88<br>(0.362) | -60.42***<br>(0.002) | -35.87*<br>(0.082) | -81.57***<br>(0.000) | -414.56***<br>(0.001) | -70.75*<br>(0.077) |
| Year | -0.37<br>(0.971) | 8.48<br>(0.684) | -4.60<br>(0.511) | 3.21<br>(0.823) | -24.98<br>(0.112) | -35.47***<br>(0.007) | -26.50<br>(0.654) | -52.18*<br>(0.079) |
| No Saharan country interacted with year | -36.76**<br>(0.010) | -86.53***<br>(0.004) | -6.50<br>(0.498) | -40.12**<br>(0.036) | -27.16<br>(0.191) | -34.58**<br>(0.035) | -562.97***<br>(0.000) | -153.30***<br>(0.000) |
| Constant | 378.97***<br>(0.001) | 361.21<br>(0.132) | 76.46<br>(0.300) | -53.56<br>(0.732) | 341.91**<br>(0.040) | 505.87***<br>(0.000) | 4259.07***<br>(0.000) | 840.47***<br>(0.003) |
| Observations | 300 | 301 | 267 | 325 | 371 | 397 | 324 | 194 |
| R squared | 0.1023 | 0.2858 | 0.0219 | 0.1261 | 0.0663 | 0.2944 | 0.4753 | 0.4239 |

## Generic annual cost

| Explained variable: Generic annual cost | Zidovudine | Didanosine | Stavudine | Lamivudine | Nevirapine | Efavirenz | Lopinavir + Ritonavir | Tenofovir |
|---|---|---|---|---|---|---|---|---|
| Log income p.c. | 6.70**<br>(0.027) | 0.01<br>(0.721) | 0.13<br>(0.952) | 11.11***<br>(0.001) | 8.70**<br>(0.048) | 3.84<br>(0.643) | 66.30**<br>(0.060) | -3.10***<br>(0.000) |
| Sub-Saharan Africa | 28.00<br>(0.226) | 73.47<br>(0.407) | -39.02**<br>(0.024) | 52.35**<br>(0.035) | 28.56<br>(0.387) | 59.22<br>(0.335) | -890.20***<br>(0.002) | 10.31<br>(0.881) |
| Compulsory lic. | 9.44<br>(0.734) | -0.22<br>(0.598) | -4.28<br>(0.830) | -10.01<br>(0.749) | -20.20<br>(0.661) | -24.27<br>(0.714) | -49.31<br>(0.901) | 104.23<br>(0.092) |
| Number of generics in the country | 18.24***<br>(0.000) | 0.39***<br>(0.000) | 9.15***<br>(0.001) | 7.29**<br>(0.047) | 9.23*<br>(0.058) | 62.26***<br>(0.000) | 887.60***<br>(0.000) | 110.17***<br>(0.000) |
| Year | -12.13***<br>(0.000) | -0.05<br>(0.135) | -1.71<br>(0.369) | -9.08***<br>(0.001) | -17.80***<br>(0.000) | -37.41***<br>(0.000) | -61.18**<br>(0.041) | -3.52<br>(0.626) |
| No Saharan country interacted with year | 4.61<br>(0.172) | 0.04<br>(0.406) | -5.42**<br>(0.038) | 5.28<br>(0.147) | 3.70<br>(0.450) | 10.67<br>(0.235) | -109.33***<br>(0.008) | 1.51<br>(0.871) |
| Constant | 94.15<br>(0.001) | 19.50<br>(0.771) | 68.86***<br>(0.001) | -23.37<br>(0.435) | 86.03**<br>(0.029) | 256.03***<br>(0.000) | 780.58**<br>(0.017) | 63.86<br>(0.360) |
| Observations | 299 | 298 | 298 | 322 | 371 | 391 | 324 | 188 |
| R squared | 0.1183 | 0.1937 | 0.1937 | 0.0705 | 0.0946 | 0.1507 | 0.5468 | 0.4924 |

These results show some common patterns across the products investigated. The average price of the ARV drugs investigated is lower:

- if the per capita income in the country is also lower;
- when the country is in the SSA region;
- when more generics are in the market; and
- if the observation is more recent.

Regressions of branded and generic prices confirm some of these results, suggesting that some of the factors affect both branded and generic products. The same regression analysis has been performed for three combination products: lamivudine+zidovudine, lopinavir+ritonavir and lamivudine+nevirapine+stavudine. The results are consistent with those obtained for single antiretrovirals, suggesting that prices of combination products do not show a distinctive behaviour.

### 5.3.1 Interpretation of the results

Taking the overall results and those of branded and generics price together offers a number of insights.

The positive correlation between prices and income is consistent with the application of differential pricing. We find this correlation in both branded and generic prices, but as we might expect, the correlation appears to be stronger in the former. This is consistent with branded manufacturers implementing differential pricing schemes but this being less common for generic manufacturers.

The positive correlation between prices and income is more significant for newer drugs (columns to the right) than for older drugs (columns to the left). Generic entry is more pervasive in older drugs no longer protected and generic competition limits the ability of branded producers to sustain differential prices schemes. In other words, where there is effective generic competition, we would expect prices to converge on the cost irrespective of the income of the country.

Prices are lower in sub-Saharan countries, even after controlling for the level of income. This is particularly the case for branded medicines. This is likely to be because most branded manufacturers have decided not to enforce patent rights in all SSA countries, irrespective of the country's level of per capita income (and hence generic competition is more likely) and that differential prices means that these countries are offered lower prices.

The number of generics that have supplied a country in a given year is negatively correlated with branded prices, suggesting that the presence of generics in the market exerts downward pressure on prices of branded drugs. However, the number of generics appears to be positively correlated with generic prices. This result is counter-intuitive, as we would expect generic prices to be lower where a greater number of generic producers compete for the market. It is

possible that this variable suffers from reverse causality, as a result of markets with higher levels of prices attracting a higher number of generic suppliers.[217]

Prices have decreased over time, especially in countries outside sub-Saharan Africa. The time trend tends to be insignificant in sub-Saharan countries, where prices have been low for the whole period. The downward trend in prices is only significant in countries outside this region. The regression analysis does not allow us to identify the reasons behind the decrease on prices in these countries. The fact that price reductions are observed even for ARV drugs that were protected during the entire period (efavirenz, lopinavir+ritonavir and tenofovir) suggests that generic competition may not be the only factor triggering price reductions. Increasingly intense class competition among alternative ARV drugs and procurement mechanisms that reinforce buyer power may also have contributed to lower prices.

Estimates show that generic prices have decreased in all countries, while branded prices have decreased mainly in countries outside sub-Saharan Africa. This is true even for ARV drugs that were protected during the entire period (efavirenz, lopinavir+ritonavir and tenofovir). This result again suggests direct generic competition does not fully explain the decrease in branded prices observed during the last years.

We do not find a significant effect of compulsory licensing on the level of prices. Coefficients are not significant for all the products, including efavirenz and lopinavir+ritonavir for which compulsory licences have been issued in Brazil and Thailand.[218] The regression results for products that were not directly affected by compulsory licences suggest the threat of compulsory licencing also does not have a significant effect.

### 5.3.2 Prices of second-line treatments

The market for second line treatments is characterised by lower demand, given that patients are only switched to second-line treatment once they become resistant or intolerant to first-line treatment. It is therefore interesting to have a closer look at the evolution of prices of second-line treatments.

Most of the ARVs in our regression analysis are typically components of first line treatments, as was shown in Table 4 in chapter 2. At the same time, however they are also part of second line treatments as the table illustrates. Zidovudine and lamivudine, for instance, are used almost as often in second-line treatment as they are in first-line treatment. In the same class of ARVs (NRTIs), didanosine is more often used in second-line treatment than in first-line. Protease inhibitors are another main component of second-line treatments. Their use as first-line treatment is much less common than their use as second-lines in combination with NRTIs. This is for instance the case of lopinavir+ritonavir.

Lopinavir+ritonavir is one of the two preferred PI for second-line treatment according to WHO guidelines, the other being atazanavir. Lopinavir+ritonavir is in fact the PI most commonly used in second-line treatment, as was shown in Table 4. The GPRM database contains extensive data on transactions involving

**217** We have run the same regressions excluding the number of generics to check whether its inclusion might be biasing our estimates for the other variables and results are broadly robust to the exclusion of the variable.
**218** As noted in the access analysis, as only Brazil and Thailand have used compulsory licences we need to be cautious in the interpretation of this result.

lopinavir+ritonavir, which has allowed us to perform the regression analysis for this drug. Unfortunately, the GPRM database contains only very limited data covering transactions of other PIs, especially atazanavir, insufficient for regression analysis to be conducted.

By looking at the results for lopinavir+ritonavir in Table 20, we observe that the pattern that emerges from the analysis is consistent with that observed for first line treatments. Prices are positively correlated with per capita income, are higher outside SSA and have decreased over time. The presence of generic competitors reduces branded prices. Drops in prices of lopinavir+ritonavir have also been documented by other sources. Medecins Sans Frontieres (MSF) provide an overview of lowest branded and generic prices of lopinavir+ritonavir since 2007.[219]

The scarcity of data on other PIs does not allow us to cover them in detail in our analysis. However, it is interesting to look at the case of atazanavir, the other preferred PI for second-line treatment in WHO guidelines. Voluntary licenses for atazanavir were granted by BMS in 2006 to generic manufacturers (Emcure and Aspen). MSF shows that generic atazanavir has been available at least since 2009 at somewhat reduced prices. It will be interesting to monitor future developments in the market for atazanavir as data become available. The scarcity of data applies not only to PIs, but also to newer ARVs (fusion, entry and integrase inhibitors), for which demand is limited and generic versions are not yet available.

The experience with lopinavir+ritonavir seems to indicate that as the use of a PIs increases, the increased business opportunity will attract generic entry and this is likely to results in price reductions. Reduced prices then facilitate broader usage of the drug. This seems to have been the case for lopinavir+ritonavir and we would expect a similar pattern to occur for other second-line ARVs, as seems to be happening already for atazanavir.

**219** MSF (2011), "Lopinavir/Ritonavir (LPV/r)", from http://utw.msfaccess.org/drugs.

## 5.4 CONCLUSIONS

The interpretation of any statistical analysis needs to be undertaken with considerable care. The robustness of the analysis depends on the quality of the data. In this case, the GPRM data is being increasingly used in analysis of this kind and has been used in multiple published studies. However, it only covers the period after 2003 and is not representative of all purchases of ARV in every country. Indeed, as in any price comparison, this will depend on the sample of medicines examined, the exchange rate applied, etc.[220]

However, the analysis described above does provide some important results. In terms of access, we find a strong correlation between the level of access achieved over the last decade and average income, spending overall and foreign spending in particular. The level of access is lower for countries in SSA or the more recent the programme for universal access has been initiated. The reduction in the price of ARVs has been particularly important for lower income countries. We do not find a significant impact for compulsory licensing. In terms of compulsory licensing, this does not mean it did not have an effect, only that other countries were able to achieve the same level of access through other means.

Our price analysis is consistent with continuing importance of differential pricing for new medicines but that introduction of generics has lowered price significantly and narrowed the difference between countries. However, we find prices fell even in the absence of generics.

**220** For a description of the many challenges posed by international price comparisons see For example, Danzon, P. M. and Furukawa, M. F. (2008) "International prices and availability of pharmaceuticals in 2005". Health Affairs, 27(1), 221 233.

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