

THE EVOLUTION OF ACCESS TO ESSENTIAL MEDICINES FOR THE TREATMENT OF HIV/AIDS – EVIDENCE FROM 2000 TO 2015

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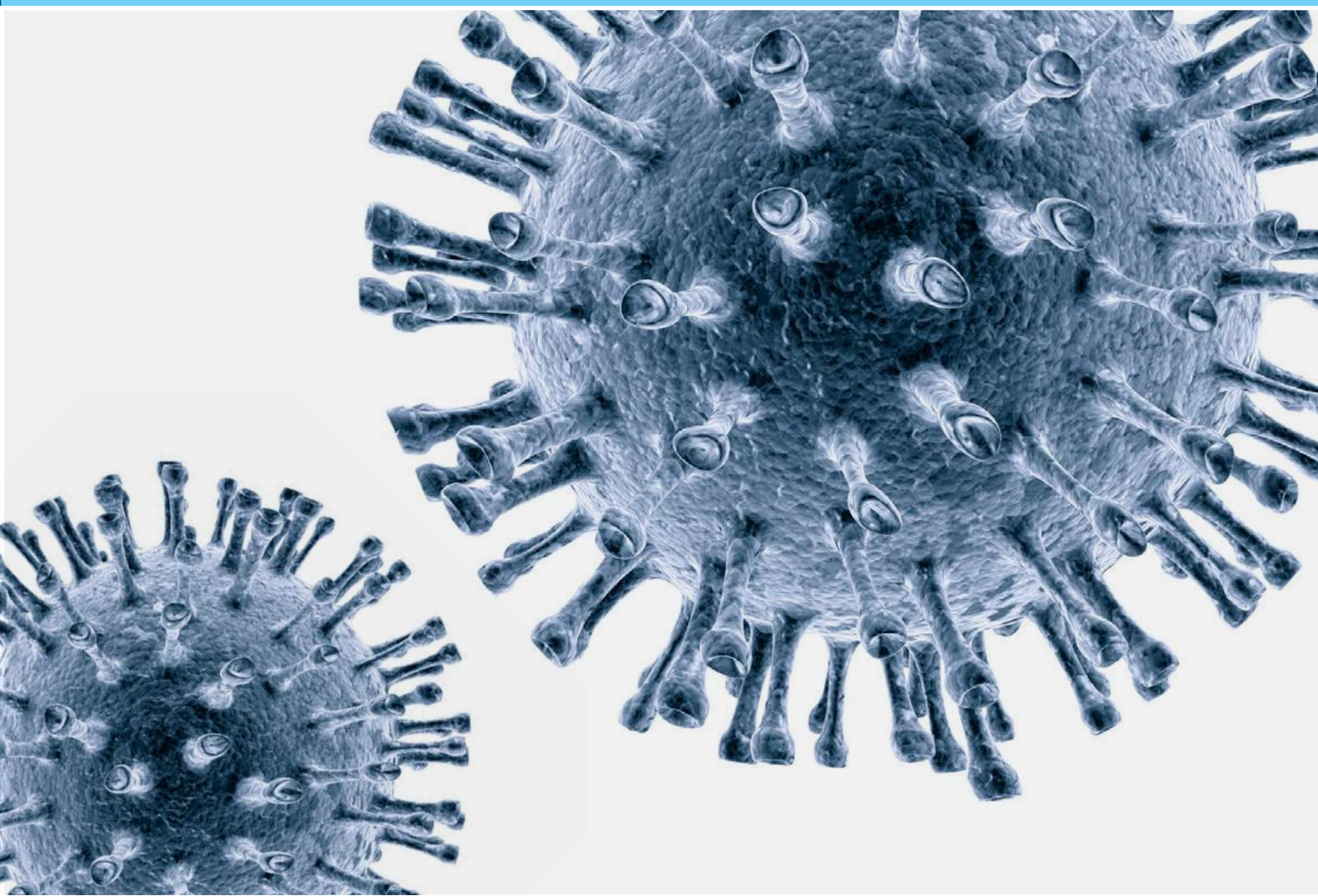


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THE INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS AND ASSOCIATIONS (IFPMA) ASKED CHARLES RIVER ASSOCIATES (CRA) TO REVIEW THE EVIDENCE ON THE FACTORS INCREASING ACCESS AND THE ASSOCIATED VALUE OF INNOVATION ACROSS LOW AND MIDDLE INCOME COUNTRIES (LICS AND MICS) FOR HUMAN IMMUNODEFICIENCY VIRUS/ ACQUIRED IMMUNE DEFICIENCY SYNDROME (HIV/AIDS) FROM 2000 TO 2015.¹

1 This builds on existing reports on “Assessing the value of radical and incremental innovation in key therapy areas in middle-income countries”, http://www.ifpma.org/fileadmin/content/Publication/2014/value_of_innovation.pdf. (2013) and “Evidence on access to Essential Medicines for the treatment of HIV/AIDS” http://www.ifpma.org/fileadmin/content/Publication/2011/CRA_Access_to_Essential_Medicines_HIV-AIDS_October2011.pdf (2011)

EXECUTIVE SUMMARY

HIV was originally identified as the likely cause of AIDS in the early 1980s, and by the turn of the century HIV/AIDS was recognised as a global health crisis. HIV/AIDS is a severe disease, and addressing it became both a national and international priority, especially for many Low Income Countries (LIC) and Middle Income Countries (MICs).² Significant steps have been taken to address this challenge over the last two decades. The purpose of this report is to present an analysis of access to medicines and the value that these medicines deliver to different countries.³

From a methodological perspective, we draw on the a large number of studies including academic international comparisons, reports by organisations such as the World Health Organisation (WHO), reports presenting the results from clinical research, and analysis undertaken as part of the clinical or economic assessment of these medicines. We have focused our analysis on a number of LICs and MICs where we can observe progress in access (specifically Botswana, Brazil, China, India, Rwanda and South Africa) over the last 15 years. We have also included a statistical analysis to test the relative importance of different factors (country characteristics and policy interventions identified in our literature search) in determining access across a much wider set of countries.

ACCESS TO TREATMENTS FOR HIV/AIDS

Over the last twenty years, the number of people living with the disease has been stabilising and the mortality and Disability Adjusted Life Years (DALYs) level has decreased significantly in the selected LICs and MICs. Furthermore, the level of transmission between mother and unborn child has decreased significantly. As set out in a recent Joint United Nations Programme on HIV/AIDS (UNAIDS) report, the progress in treating HIV/AIDS has been dramatic over the last 15 years:⁴

- New HIV infections have fallen by more than a third (35%);
- HIV/AIDS-related deaths have declined by 41%;
- The global response to HIV/AIDS has averted 30 million new HIV/AIDS infections and nearly 8 million (7.8 million) AIDS-related deaths since 2000, when the Millennium Development Goals were set.

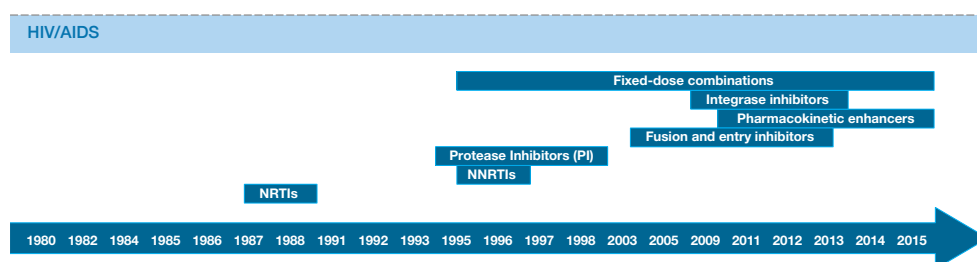
In terms of pharmaceutical innovation, the progress has also been rapid. Commercialisation of the first HIV/AIDS medicines started in the mid-to-late 1980s with the release of zidovudine, the first in class nucleoside reverse-transcriptase inhibitor. Since then, the treatment paradigm for HIV/AIDS has been developed – in the mid-1990s a new generation of antiretroviral drugs became available which was followed by the introduction of protease inhibitors (PI), non-nucleoside reverse-transcriptase inhibitors (NNRTI) and other classes of therapies (Figure 1).

2 Shao, Y & Williamson C (2012) “The HIV-1 Epidemic: Low and Middle-Income Countries.” Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3282497/>. [Accessed on 05.02.2016].

3 CRA (2011), ‘Evidence on access to Essential Medicines for the treatment of HIV/AIDS’, a report commissioned for IFPMA.

4 UNAIDS (2015) “How AIDS changed everything—MDG 6: 15 years, 15 lessons of hope from the AIDS response”. Available at: [How AIDS changed everything—MDG 6: 15 years, 15 lessons of hope from the AIDS response](http://www.unaids.org/en/mediacentre/pressreleases/2015/02/150215_How-AIDS-changed-everything-MDG-6-15-years-15-lessons-of-hope-from-the-AIDS-response). [Accessed on 05.02.2016].

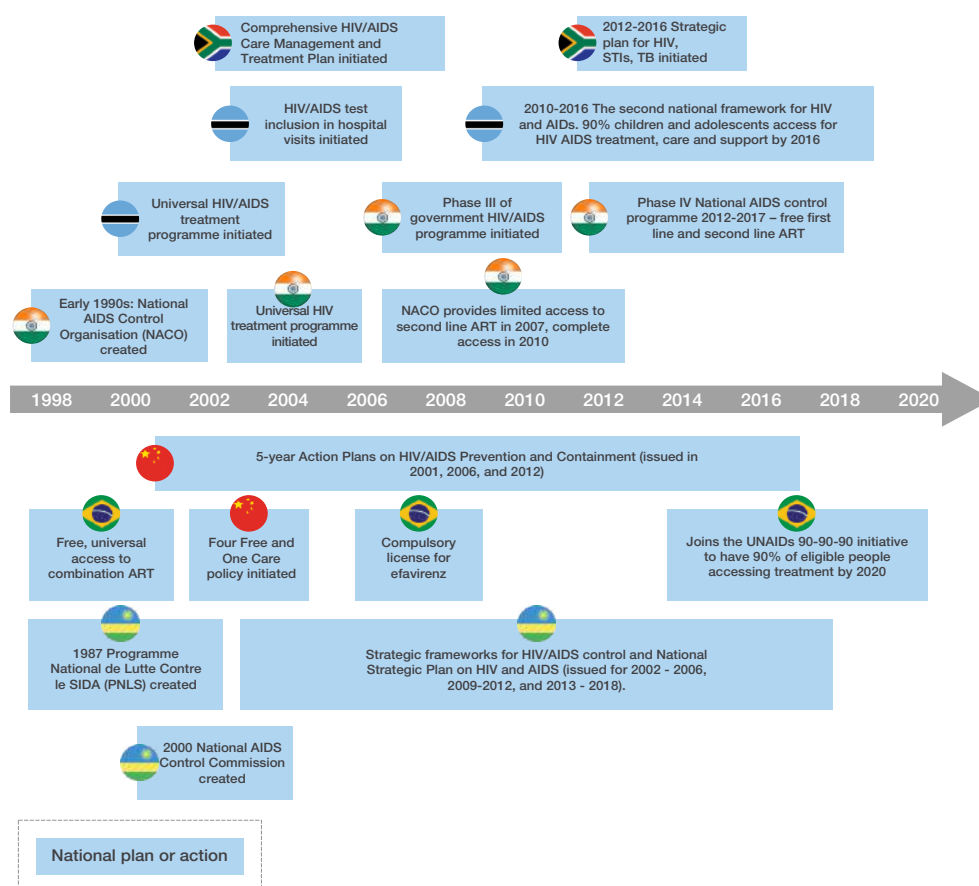
Figure 1: Classes of therapy for HIV



Source: CRA analysis

Recognising the importance of access to HIV/AIDS treatments, often working with international organisations and NGOs, the selected LICs and MICs have developed national strategies to control HIV/AIDS. We observed that all the selected countries have undertaken national initiatives (Figure 2). Brazil, Botswana and Rwanda spear-headed national initiatives but as of 2015, all countries in this report have developed and renewed national strategies to address the burden of HIV/AIDS.

Figure 2: Timeline of national strategies against HIV/AIDS in BICS + Botswana



Source: CRA analysis

We find a general increase in access to ARTs across countries although it is acknowledged that some population groups continue to face significant challenges in access to ART.^{5,6,7,8,9}

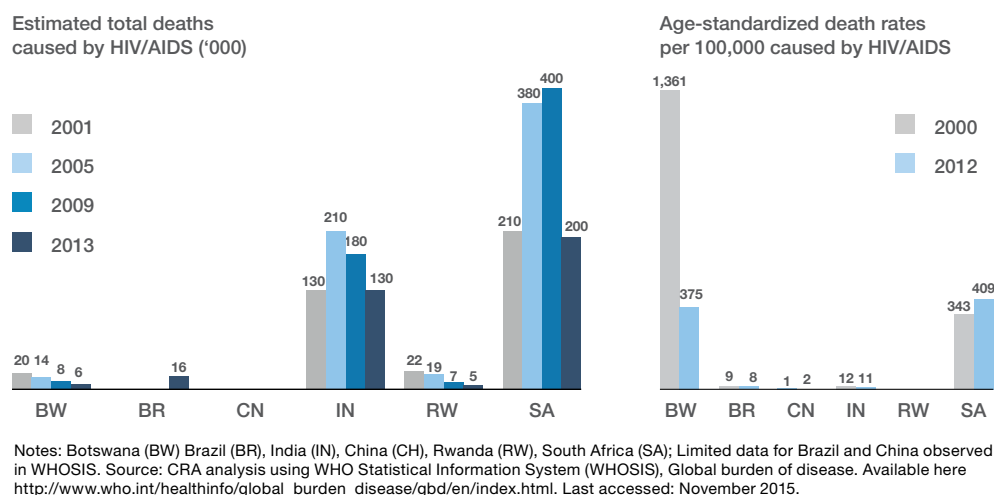
To understand the factors determining access to ART, we conducted a review of six LIC and MIC case studies and a statistical analysis with a much larger scope of LICs and MICs. We find that a country's prioritisation of HIV (represented as the start of ART programmes) is correlated to the level of ART coverage (even though many of the countries initiated these programmes some years ago). This illustrates the continuing progress made by all countries (often encouraged by international organisations and NGOs) but also the time taken to catch-up in terms of coverage. Indeed, many countries have refreshed and updated their plans over time. The investment in health care infrastructure is clearly also important with the spending on health and HIV/AIDS specifically positively associated with ART coverage (although the relative importance differs depending on the wealth of the country). The substantial increase in resources from the international community that has been dedicated to promoting health over the last several years has changed 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. MICs have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit. As in our 2011 analysis we do not find intellectual property (as proxied by whether a country has used compulsory licensing) to be an important determinant of access to ART. Drawing on the case studies, the innovative industry has contributed to the affordability of ART through voluntary licensing and differential pricing, which emerged as a common practice at the beginning of the decade. At the same time, generic manufacturers, often using voluntary licence agreements, have played an important role in all of the case studies. For example, this has meant that Saharan Africa countries like Rwanda and South Africa have been able to supply a large proportion of first line ARTs with generic alternatives.¹⁰

THE VALUE OF TREATMENTS FOR HIV/AIDS

Turning to the evidence on the value of these treatments in helping to address to HIV/AIDS epidemic. Evidence on the clinical benefit of access to HIV/AIDS treatment has grown over the last 15 years. We find across the LICs and MICs the number of deaths associated with HIV/AIDS has declined over the years (Figure 3).

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- 5 The Body (2009). "Many Chinese Children living with HIV do not have treatment access". Available at: <http://www.thebody.com/content/art51368.html> [Accessed 16.05.2016]
 - 6 Infochange. "India launches national paediatric HIV/AIDS". Available at: <http://infochangeindia.org/public-health/news/india-launches-national-paediatric-hiv-aids-initiative.html> [Accessed 16.05.2016].
 - 7 Mothi, S.N. et al (2011). Paediatric HIV – trends and challenges. Indian J Med Res 134; pp 912-919. Available at: <http://icmr.nic.in/ijmr/2011/december/1214.pdf>. [Accessed 16.05.2016].
 - 8 AVERT (2013). "HIV and AIDS in Botswana" Available at: <http://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/botswana>. [Accessed 16.05.2016]
 - 9 MindText (2010). "Impact of HIV/AIDS on the Indian economy". Available at: http://www.mindtext.org/view/86/Impact_of_HIV/AIDS_on_the_Indian_economy/. [Accessed 16.05.2016]
 - 10 Between 2004 and 2006, the total percentage of first line ARVs procured = 65% generic, 35% branded. Chien, C (2007), "HIV/AIDS drugs for sub-Saharan Africa: How do brand and generic supply compare." Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1805689/>

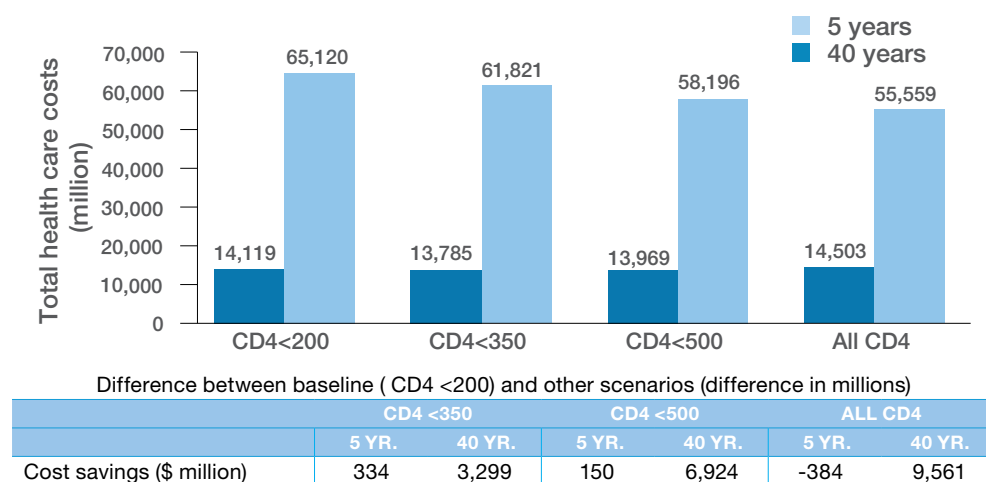
Figure 3: Burden of HIV/AIDS within selected countries



It is evident that access to antiretroviral drugs (ARVs), in combination with improvements in prevention and diagnosis, has played a significant role. Access to improved fixed-dose combinations (FDCs) is likely to have had a positive impact in markets where they are available (due to increased adherence) although currently, there is a lack of published evidence in this area.

In addition to clinical and therapeutic benefits, there is also evidence that the introduction of these policies and access to ART is beneficial economically, through the reduction in other healthcare costs (such as hospitalisations), and socio-economically, through reduction of absenteeism and improvements in HIV/AIDS patients' quality of life. One study demonstrated ART coverage for a larger population has economic benefits in South Africa (Figure 4). In this study, if all patients were diagnosed and treated immediately with ART, overall costs of HIV care would decrease by \$10 billion over a 40-year period, with a breakeven point reached by 2023. It is notable that the data on the economic benefits has often focused on employer sponsored programmes, illustrating the importance of the private sector in improving access.

Figure 4: Economic effects of extending the ART eligibility criteria in South Africa



Source: Granich R et al. (2012) Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050, PLOS ONE, Vol. 7, no. 2. Note: All CD4 levels scenario involves offering ART to everyone immediately after diagnosis with HIV irrespective of CD4 count

POLICY IMPLICATIONS

Drawing on the evidence for the value of innovation in HIV/AIDS, and after an analysis of the policies adopted across LICs and MICs, we have also reviewed the policy implications from our earlier studies:

- 1. A national disease awareness programme is critical to ensuring that the widest population benefits from the value of innovative medicines** – Encouraged by NGOs and supported by international organisations, governments around the globe have implemented national strategies aimed at controlling the HIV/AIDS epidemic by preventing transmission and providing access to treatment. Across countries in this report, improvements in ART coverage were initiated by these national plans –prior to 2000 in Brazil, Botswana and Rwanda and soon after in the early 2000s in China, India and South Africa. The national plans identified HIV/AIDS as a priority for the government and are associated with increased resources assigned to ensure access to treatment, although the source of funds differs with some receiving financial help from transnational organisations like the World Bank and the Bill and Melinda Gates Foundation (Rwanda), while in others domestic spending has played a greater role (China, Botswana, and South Africa). Maintaining the focus over time through updating and refreshing these programmes appears important. Considering the estimate that an additional 28 million people could be living with HIV by 2030 if current coverage rates are not improved, it remains vital that these countries, and in particular MICs like India and China, maintain HIV as a national priority.¹¹ Indeed, the need to keep HIV/AIDS at the forefront of national policies has been advocated by the WHO and UNAIDS.^{12,13,14}
- 2. Appropriate healthcare infrastructure and integrated programmes that ensure diagnosis, testing, access to medicines and keeping patients on a course of treatment are necessary for medicines to fully deliver value.** – The appropriate provision of ART to patients with HIV/AIDS is associated with investing in healthcare infrastructure. Without patients being identified, diagnosed, tested and appropriately managed, it is not possible to increase access and, unsurprisingly, we are then unlikely to observe benefits from medicines in LICs and MICs. Unsurprisingly, countries that devote more spending on health and HIV related services are associated with greater ART coverage, which in turn, contributes to the accumulation of value from ART. For example, Botswana's early introduction of universal health coverage for ART significantly increased access to HIV treatment and reaped a reduction in the prevalence of HIV.¹⁵ As evidenced by the importance of the “age” of the programme in increasing access, this investment

11 The Times of India (2016). “Budget cuts for NACO hits HIV/AIDS control programme” Available at: <http://timesofindia.indiatimes.com/city/visakhapatnam/Budget-cut-for-NACO-hits-HIV/AIDS-control-programme/article-show/52286050.cms>

12 WHO (2014) “HIV, universal health coverage and the post-2015 development agenda – A discussion paper”. Available at: <http://www.who.int/hiv/pub/toolkits/universal-coverage2014/en/>. [Accessed 08.02.2016].

13 UNAIDS (2015). “How AIDS changed everything – MDG6 15 years, 15 lessons of hope from the AIDS response.” Available at: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf. [Accessed on 08.02.2016].

14 UNAIDS (2016), “Fast-track Ending the AIDS Epidemic by 2030.” Available at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.

15 WHO (2014), “Country Cooperation Strategy – Botswana.” Available at: http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_bwa_en.pdf. [Accessed on 08.03.2016].

needs to be maintained over time. This is consistent with the increasing importance of tackling other diseases. The value of developing the healthcare infrastructure to combat HIV extends to other diseases. Healthcare centres built to diagnose and distribute ART and the infrastructure to facilitate patient access to those centres also helps address other infectious and non-communicable diseases. With the UNAIDS goals to increase access to 90% of all HIV patients by 2020 and 95% by 2030, the need for continued and increased spending on HIV/AIDS to build capacity in HIV management and services is clear (as recommended in recent reports by international organisations).^{16,17,18}

3. **The system needs to incorporate both patented and off-patent products delivering value to patients, the healthcare system and society** – Innovators have been responsible for all of the significant new medicines treating HIV over the last decade. However, both the generic industry and the innovative industry have and continue to contribute in different ways to addressing the epidemic. In some situations, generic companies are able to supply low-income countries more efficiently and more cheaply than innovating companies. Equally, innovative companies have introduced different approaches (working collaboratively where appropriate) to increase access to their medicines. To this end, we have seen that voluntary licensing and differential pricing are increasingly common. Despite the concern that intellectual property rights can impede access to HIV treatment, we find very few examples of compulsory licensing in LICs and MICs over the last decade. Moreover, in our statistical analysis, we do not find there to be any relationship with their use and the extent of ART coverage. Instead, we find there is an increasing trend in the use of voluntary licensing and that both patented and off-patent products have a role to play in delivering value to LICs and MICs. Looking ahead, we expect the generic and innovative industry to continue with their roles in improving access to HIV medicines. There is an obvious need for the innovative industry to continue investing in the development of new therapies for HIV.

4. **In LICs and MICs, the value medicines needs to be considered holistically as they deliver value directly to patients, to the healthcare system, and to the wider society** – ART have delivered a broad range of benefits affecting not only patients but also the healthcare system and the society in general. We found evidence of value being delivered through reduced healthcare costs and through benefits to the wider economy. In South Africa, we observed clinical benefits, healthcare cost savings and large societal benefits in terms of reduced absenteeism. Similar to South Africa, we observed productivity gains in India and Botswana due to ART. In terms of allocating resources to HIV/AIDS, a holistic approach taking into account the full range of benefits is important.

16 UNAIDS (2016), "Fast-track Ending the AIDS Epidemic by 2030." Available at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.

17 WHO (2014) "HIV, universal health coverage and the post-2015 development agenda – A discussion paper". Available at: <http://www.who.int/hiv/pub/toolkits/universal-coverage2014/en/>. [Accessed 08.02.2016].

18 UNAIDS (2015). "How AIDS changed everything – MDG6 15 years, 15 lessons of hope from the AIDS response." Available at: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf. [Accessed on 08.02.2016].

CONCLUSION

The purpose of this paper was to analyse the determinants of access to ART and the evidence that innovative medicines have delivered value in LICs and MICs. It is evident that access to ART, in combination with improvements in prevention and diagnosis, has played a significant role. Access to improved FDCs is likely to have had a positive impact in markets where they are available, due to increased adherence. In addition to clinical and therapeutic benefits, there is also evidence that the introduction of these policies and access to ART is beneficial economically, through reduction in other healthcare costs (such as hospitalisations), and socio-economically, through reduction of absenteeism and improvements in the patient's quality of life.

The relevance of our policy implications extends to the next phase in the battle against HIV. As the UN aim is to ensure at least 90% of all people with HIV have access to ART by 2020 and end the AIDS epidemic by 2030 (UN Sustainable Development Goals), it will be critical to continue national strategies prioritising HIV and maintaining innovation in the field of HIV treatments.^{19, 20} Data collection on the clinical and economic impact of HIV/AIDS treatment will be imperative in providing a continued rationale to tackle HIV/AIDS.

Finally, increasing access to HIV/AIDS treatment has come about due to the action of many different stakeholders. NGOs have encouraged policymakers to prioritise action, international organisations have provided funding, expertise and facilitated collaboration between companies, national policymakers have recognised the problem and prioritised the building of healthcare infrastructure, and the innovative and generic industry have played a vital role in developing and helping to provide access to medicines. In addition to addressing HIV, these efforts have clearly contributed to combatting other diseases and provided important policy lessons regarding the development of Universal Health Coverage.^{21,22,23} To this end, the policy implications we detail in this report have relevance beyond access to HIV/AIDS treatment.

19 UNAIDS (2014), "90-90-90 An ambitious treatment target to help end the AIDS epidemic." Available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. [Accessed on 01.02.2016].

20 UN (2015), "Sustainable Development Goals." Available at: <https://sustainabledevelopment.un.org/?menu=1300>. [Accessed on 08.03.2016].

21 WHO (2014), "HIV, Universal Health Coverage and the post-2015 development agenda: a discussion paper." Available at: http://apps.who.int/iris/bitstream/10665/128120/1/9789241507530_eng.pdf. [Accessed on 08.03.2016].

22 Lamptey, P and Dirks, R (2012), "Building on the AIDS response to tackle NCDs". Available at: <http://www.commonwealthhealth.org/wp-content/uploads/2012/05/9-13.pdf>. [Accessed on 08.03.2016].

23 Marquez, P (2014), "HIV/AIDS: A linchpin for Universal Health Coverage." Available at: <http://blogs.worldbank.org/health/hivaids-linchpin-universal-health-coverage> [Accessed on 08.03.2016].

1

INTRODUCTION

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) asked Charles River Associates (CRA) to review the evidence on the factors increasing access and the associated value of innovation across Low and Middle Income Countries (LICs and MICs).

1.1. BACKGROUND

Over the last ten years, the industry and academia have put together a range of evidence on the value that medicines bring to society. There have been papers setting out the different components of innovation,²⁴ studies attempting to quantify aggregate benefits that new medicines bring²⁵ and studies looking at the range of case studies illustrating the value that medicines deliver during the patented period.²⁶ In each of these areas, there is now a body of evidence in the United States (US) and increasingly in European markets regarding the value of innovation in terms of case studies and empirical evidence. However, there is relatively little evidence on the value of innovation in emerging markets.²⁷ This report is intended to complement and build upon the existing IFPMA-commissioned research publications on innovation and access.²⁸

This report looks at the case of Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS). It is timely to review the evidence on HIV/AIDS, given the role played by the Millennium Development Goals (MDGs).²⁹ These represented targets for 2015 and are attributed with guiding international development policies and investments and having a significant impact on health policy around HIV/AIDS. There have been a series of reports setting out the progress that has been made,³⁰ with UNAIDS announcing that the goal of 15 million people on life-saving HIV/AIDS treatment by 2015 has been met nine months ahead of schedule.³¹

The progress in treating HIV/AIDS has been dramatic, according to UNAIDS since the beginning of the 21st century:³²

- New HIV infections have fallen by more than a third (35%);
- HIV/AIDS-related deaths have declined by 41%;

24 'The Many Faces of Innovation' by OHE Consulting for the European Federation of Pharmaceutical Industries and Associations (EFPIA), 18 February 2005.

25 Lichtenberg, 2010, 'The Contribution of Pharmaceutical Innovation to Longevity Growth in Germany and France' CESifo Working Paper Series No. 3095 or Lichtenberg, 2003, 'The Impact of New Drug Launches of Longevity: Evidence from Longitudinal, Disease-level Data from 52 Countries, 1982-2001', NBER Working Paper Series.

26 PhRMA 'Pharmaceutical Industry profile'.

27 The exceptions to this are the IFPMA report 'Incremental Innovation: Adapting to patient needs', February 2013, and the recent project undertaken by Charles River Associates on behalf of PhRMA. This takes a different approach by cataloguing examples of incremental innovation that have been aimed at addressing specific challenges in emerging markets.

28 This includes IFPMA reports 'Pharmaceutical R&D Projects to Discover Cures for Patients with Neglected Conditions' and 'Policies that encourage innovation in middle-income countries'.

29 In particular, Millennium Development Goal 6a to have halted by 2015 and begun to reverse the spread of HIV/AIDS.

30 World Health Organisation (2015) "HIV, Universal health coverage and the post-2015 development agenda: A discussion paper"

31 Press release "UNAIDS announces that the goal of 15 million people on life-saving HIV treatment by 2015 has been met nine months ahead of schedule"

32 UNAIDS (2015) "How AIDS changed everything—MDG 6: 15 years, 15 lesson of hope from the AIDS response"

- The global response to HIV/AIDS has averted 30 million new HIV/AIDS infections and nearly 8 million (7.8 million) AIDS-related deaths since 2000, when the MDGs were set.

This report considers the role played by improved access to antiretroviral therapy (ART).

1.2. OUR APPROACH

While there exists a large amount of statistical evidence on the impact and value of antiretroviral medication across countries, we focus on evidence from countries where we can observe improvements in access: Botswana, Brazil, China, India, Rwanda and South Africa.^{33, 34} In order to better understand the impact of antiretroviral medication on populations with HIV/AIDS in these countries, we draw on existing academic and policymaker literature. The literature review is based on a combination of the following key search terms: “impact, value, cost, cost savings, cost-effectiveness, hospitalisations, burden” and “antiretrovirals/treatment for HIV/AIDS” and “Botswana, Brazil, China, India, Rwanda and South Africa”. The literature search was conducted on PubMed and Google Scholar and covered the last 15 years. A statistical analysis has also been undertaken including a much wider set of countries (including countries where there has been much less progress in terms of improving access to ART).

1.3. THE STRUCTURE OF THE REPORT

The remainder of the report is structured as follows:

- First, we look at the evolution of the treatment options for HIV/AIDS, the extent to which treatments are actually available and accessible within the selected markets and the evidence available regarding the added value that treatment has brought to LIC and MICs.
- Secondly, we consider the policy implications.

33 This allows us to compare progress made since our earlier studies conducted in 2011 and 2013. In CRA (2011), ‘Evidence on access to Essential Medicines for the treatment of HIV/AIDS’, a report commissioned for IFPMA we looked Rwanda, India, Thailand, Botswana, Brazil, Mexico, South Africa. In November 2013. “Assessing the value of radical and incremental innovation in key therapy areas in middle-income countries” we examined the situation in Botswana, Brazil, China, India and South Africa.

34 While we look at these six case study countries that have clearly made progress in access to ARVs, we acknowledge that it is equally useful to examine countries that have made less progress. To this end, we have included a wide range of LICs and MICs in our econometrics analysis.

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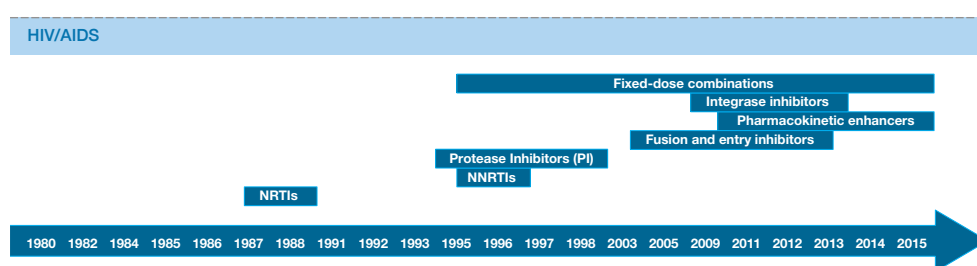
ACCESS TO HIV/AIDS TREATMENTS

HIV was originally identified as the likely cause of AIDS in the early 1980s, and within the following two decades, HIV/AIDS was recognised as a global health priority. Despite HIV/AIDS being a global epidemic, the biggest challenge was faced by LIC and MICs (particularly in Sub-Saharan Africa).³⁵ After briefly reviewing the development of medicines, we have looked at policies applied to control HIV/AIDS, access to antiretroviral therapy (ART), and the evidence on the value that these treatments have delivered.

2.1. EVOLUTION OF TREATMENT OPTIONS FOR HIV/AIDS

HIV/AIDS was clinically recognised for the first time in 1981 and hence is a relatively recent disease.³⁶ Over the last thirty years, a number of new classes of medicines have been developed. In addition, pharmaceutical companies have developed novel drug combinations (Figure 5).

Figure 5: Classes of therapy for HIV



Source: CRA analysis

Commercialisation of the first HIV/AIDS medicines started in the mid-to-late 1980s with the release of zidovudine, the first in class nucleoside reverse-transcriptase inhibitor. The treatment paradigm for HIV/AIDS was developed in the mid-1990s when a new generation of antiretroviral drugs became available. This was followed by the introduction 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 monotherapy.³⁷ This kind of 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-boosted PI). This is summarised in Figure 6.

Antiretroviral therapy is broadly classified by the phase of the retrovirus life cycle that the therapy inhibits:

- **Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI)** inhibit reverse transcription by being incorporated into the newly synthesised viral DNA

35 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

36 Gallo R (2006) 'A reflection on HIV/AIDS research after 25 years', *Retrovirology*, 3, 72.

37 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

strand as a faulty nucleotide. This causes a chemical reaction resulting in DNA chain termination.³⁸ Examples of NRTIs include tenofovir and zidovudine.

- **Non-nucleoside reverse transcriptase inhibitors (NNRTI)** inhibit reverse transcriptase directly by binding to the enzyme and interfering with its function. Examples of NNRTIs include nevirapine and efavirenz.³⁹
- **Protease inhibitors (PIs)** target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new virions. Examples of PIs include atazanavir, ritanovir and lopinavir. Ritonavir is often used to boost other PIs.
- **Entry inhibitors (or fusion inhibitors)** targets the initiation processes of the viral infection by interfering with the binding, fusion and entry process of HIV-1 to the host cell by blocking one of several targets. Two molecules, maraviroc and enfuvirtide, are the only two entry inhibitors that are currently available.⁴⁰
- **Integrase inhibitors inhibit** the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell (an important step for viral replication). There are several integrase inhibitors currently under clinical trial, and raltegravir became the first to receive FDA approval in October 2007. This includes raltegravir, elvitegravir and dolutegravir.⁴¹
- **Pharmacokinetic enhancers** increase the amount of other HIV medicines in the blood. Specifically, when used in combination with other HIV medicines (atazanavir and darunavir), pharmacokinetic enhancers interfere with or slow down the breakdown of the other HIV medicine in the body. This means there is an increase in antiviral levels in the blood stream of these other HIV medicines, thereby also an increase in their antiviral activity.⁴²
- **Fixed-dose combination (FDC)** with respect to ART refers to a pill that combines two or more ARTR into a single-dose pill. Combinations may also include ritonavir-boosted PIs, where the ritonavir is used in conjunction with another PI to boost the effect of the latter. Examples include efavirenz + tenofovir + emtricitabine, zidovudine + lamivudine and lopinavir + ritonavir (the latter is ritonavir-boosted PI).

38 Das and Arnold (2013), 'HIV-1 reverse transcriptase and antiviral drug resistance. Part 1', *Current Opinion in Virology*, 3, 2.

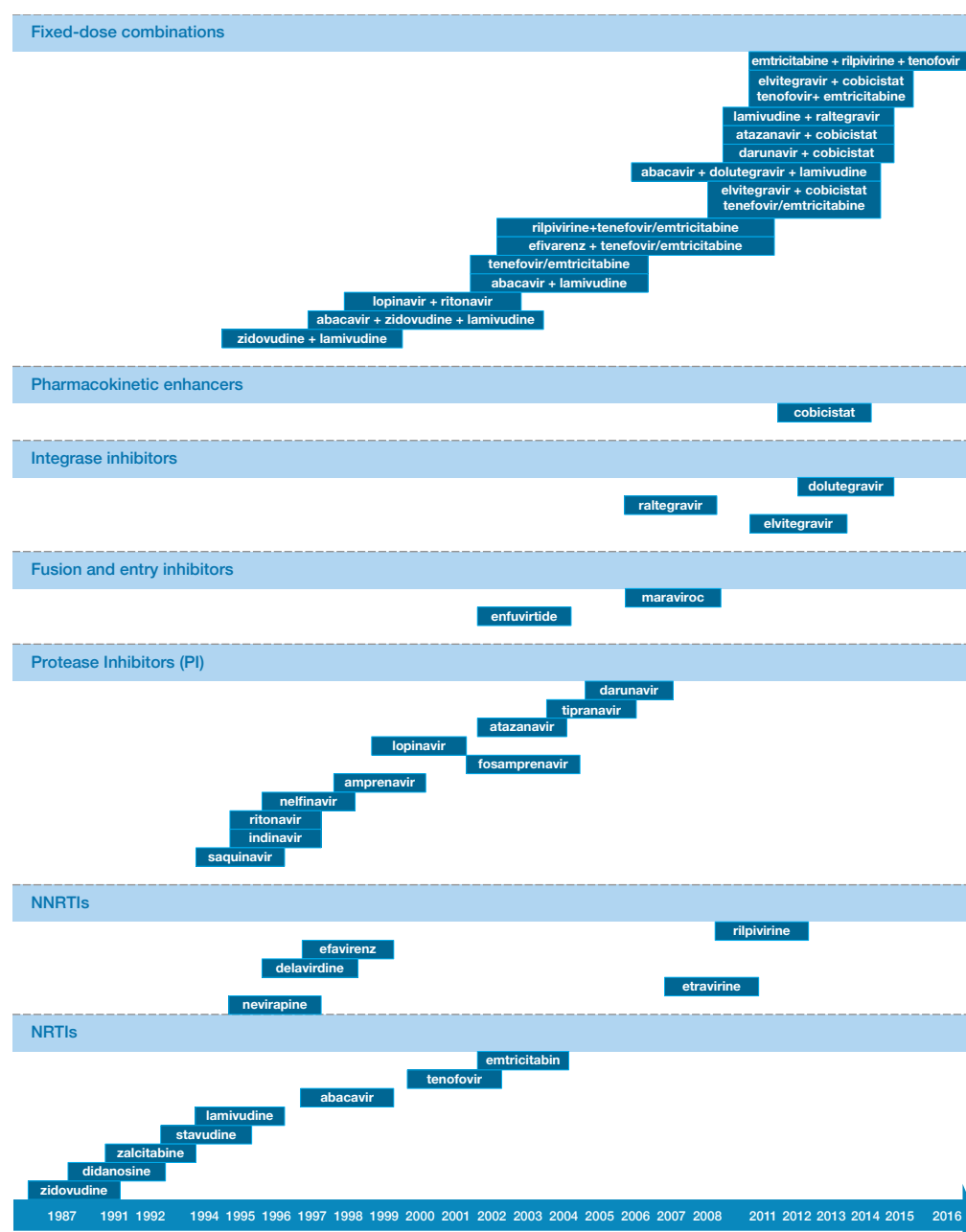
39 Ibid.

40 De Feo and Weiss (2012), 'Escape from Human Immunodeficiency Virus Type 1 (HIV-1) Entry Inhibitors', *Viruses*, 4, 12.

41 Kessl, et al (2012), 'Multimode, Cooperative Mechanism of Action of Allosteric HIV-1 Integrase Inhibitors', *Journal of Biological Chemistry*, 287, 20.

42 AIDSinfo (2015), "Cobicistat". Available at: <https://aidsinfo.nih.gov/drugs/536/cobicistat/0/patient>. [Accessed on 20.11.2015].

Figure 6: Development of new ART over time by class



Source: CRA analysis using Decision resources HIV product portfolio Note: these are the individual stand-alone products. Approved drug combination therapy is not included in this timeline. NRTI – Nucleoside and nucleotide reverse transcriptase inhibitors; NNRTI – Non-nucleoside reverse transcriptase inhibitors

RECOMMENDED TREATMENT FOR HIV/AIDS IN WHO GUIDELINES

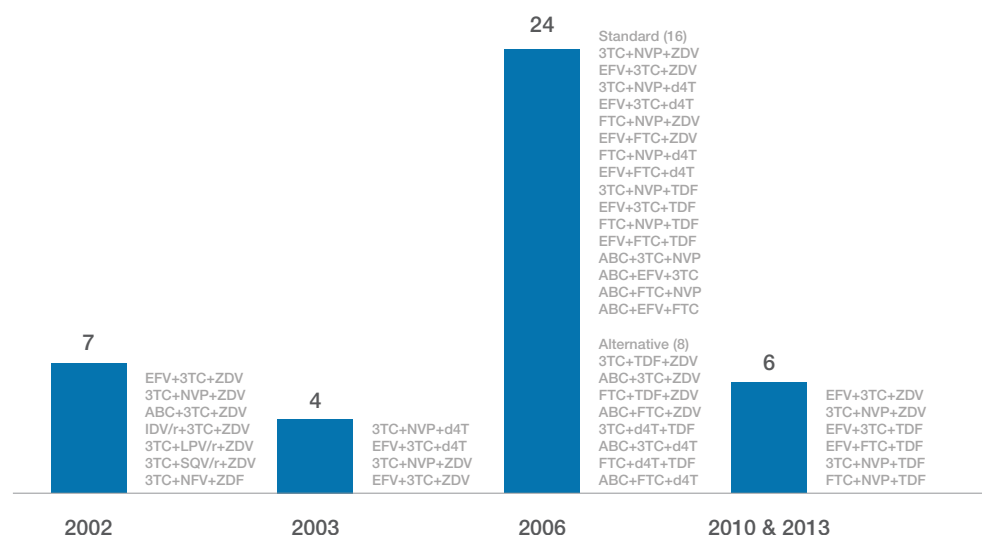
- Since the first WHO guidelines for HIV/AIDS treatment were published in 2002, first and second line ART have been revised on a number of occasions. Regular updates of treatment guidelines are an expected consequence of the significant advances made by researchers in the field over the last several years.⁴³ The next consolidated guideline on the use of ART will be published in 2016.⁴⁴ Changes in first-line ARTs recommended by WHO are displayed Figure 7 below and summarized below:

43 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.

44 WHO (2015). "Guideline on when to start antiretroviral therapy and pre-exposure prophylaxis for HIV". Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1

- The **first WHO HIV/AIDS guidelines** were released in 2002. WHO recommended seven regimens, all of which were based on the use of zidovudine, the first NRTI, which became available in the late 1980s, and lamivudine. Different types of combinations were also recommended: 3 NRTIs, 2 NRTIs plus 1 NNRTI, and 2 NRTIs plus 1 PI.
- The **first revision of WHO guidelines**, published in 2003, reduced the number of recommended first-line treatments to four combinations of the same type, 2 NRTIs plus 1 NRT. It also 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, a **second revision of WHO guidelines** was released, which included 16 standard regimens and 8 additional alternative regimens, almost all of which utilised 2 NRTIs plus 1 NRTI. This revision incorporated two new NRTIs, emtricitabine and tenofovir. The 2006 guidelines also suggested moving away from older regimens due to related toxicities.
- A **third revision of WHO guidelines** in 2010, reduced the number of recommended first-line treatments to just six combinations, excluding stavudine-based treatments.^{45,46}
- A **fourth revision in 2013** did not change the first line treatment recommendations for adults (6 alternative remain).⁴⁷

Figure 7: Recommended first-line ART in WHO guidelines



Source: WHO Antiretroviral therapy for HIV infection in adults and adolescents 2010 revision; 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; WHO (2013). "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" available at <http://www.who.int/hiv/pub/guidelines/arv2013/en/>; Note: EFV – efavirenz, 3TC – lamivudine, ZDV – zidovudine, NVP – nevirapine, ABC – abacavir, IDV/r – indinavir/ritonavir, LPV/r – lopinavir/ritonavir, SQV/r – saquinavir/ritonavir, d4T – stavudine, FTC – emtricitabine, TDF – tenofovir

- 45 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).
- 46 WHO (2010) 'Antiretroviral therapy for HIV infection in adults and adolescents – Recommendations for a public health approach 2010 revision', World Health Organization.
- 47 WHO (2013). "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection" available at <http://www.who.int/hiv/pub/guidelines/arv2013/en/>

The largest change in the new recommendations was to encourage all countries to initiate treatment in adults living with HIV when their Cluster of differentiation 4 (CD4) cell count falls between 350 and 500 cells/mm³ or less.⁴⁸ In 2014, the WHO further published a supplement to the guidelines on the use of antiretroviral drugs for treating and preventing HIV infection which confirmed that two HIV medicines – lamivudine (3TC) and emtricitabine (FTC) are interchangeable.⁴⁹ Most recently in 2015, the WHO has recommended the start of antiretroviral therapy on adults and adolescents with HIV and at all CD4 counts.^{50, 51} These WHO guidelines have played an important role in encouraging efforts to increase access to ART. Indeed, we find that within a few years of 2010 WHO guideline revisions, 90% of all countries had adopted the new recommendations and so a wider HIV population became eligible for treatment.

Turning to HIV/AIDS detection, treatment and monitoring, we find that pathways have been widely defined. To illustrate how this is meant to be applied we use the patient treatment pathway followed in Botswana to illustrate the steps that are typically recommended.

In Botswana, patients are first screened and tested using the ‘double rapid’ or ELISA test; this should be available in all clinical and outreach settings throughout the country. Patients diagnosed with HIV/AIDS should promptly have CD4 and clinical screening to determine eligibility for ART and other opportunistic infection medication (patients with severe cases of HIV/AIDS will be given prophylaxis medicines against other pathogens).⁵²

Patients eligible for ART commence first-line treatment, which includes two NRTIs and one NNRTI.⁵³ If patients are intolerant of the NNRTI, they are switched to a PI whose selection is based on various criteria. Patients who fail first-line treatment are placed on second-line treatment. Again, this follows WHO 2010 guidelines and includes two NRTIs and one NNRTI. During the first two years of ART, patients are monitored carefully and are scheduled for a check-up every three months. These steps are summarised in Figure 8.

48 The previous WHO recommendation, set in 2010, was to offer treatment at 350 CD4 cells/mm³ or less.

49 WHO (2014). “March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.” Available at: http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_march2014/en/. [Accessed on 16.11.2015].

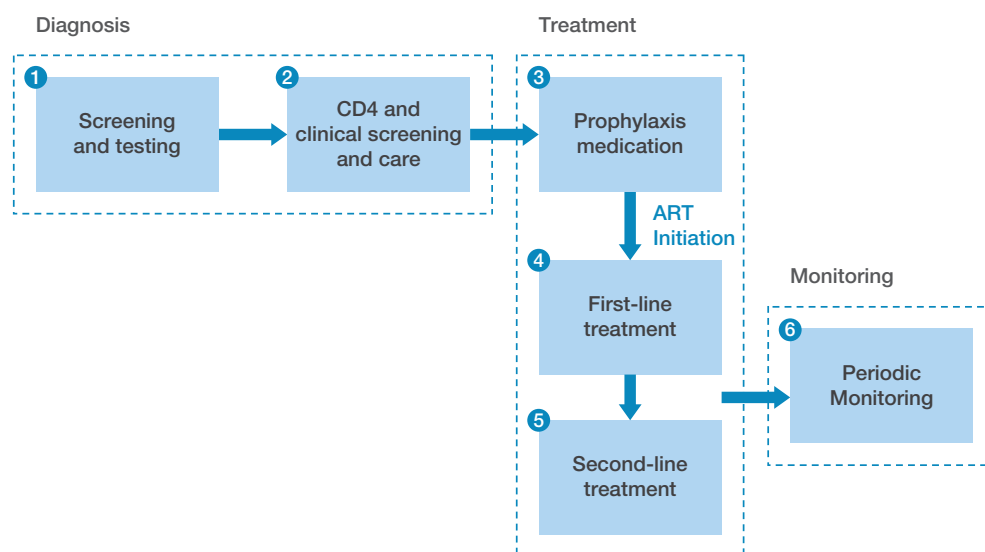
50 WHO (2015), “Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV.” Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1. [Accessed pm 20.11.2015].

51 The 2015 WHO recommendations have succeeded the 2014 WHO recommendation that ART should be initiated in all individuals with CD4 count <500 cells/mm³. See WHO (2014) “Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations.” Available at: http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1

52 Botswana Ministry of Health (2012) ‘Botswana National HIV & AIDS treatment guidelines’.

53 These are the class combinations recommended by WHO in its 2010 guidelines.

Figure 8: HIV/AIDS treatment pathway in Botswana



Source: Botswana Ministry of Health (2012) Botswana National HIV & AIDS treatment guidelines

2.2. ACCESS TO MEDICINES FOR HIV/AIDS

In this section, we summarise the national strategies introduced by the selected countries to fight against HIV/AIDS and then look at the access to these treatments.⁵⁴

NATIONAL STRATEGIES APPLIED TO CONTROL HIV/AIDS

HIV/AIDS has been of great concern for LICs and MICs, leading governments to introduce and implement specific national HIV/AIDS strategies. Although different policies have been applied, all governments had a similar goal: to control the HIV/AIDS epidemic by preventing transmission and providing access to treatment.

- In 1999 the President of the Republic of **Botswana** declared HIV/AIDS to be a national emergency. Shortly after, in 2001, Botswana became the first country in Africa to offer ART to universal health coverage for ARVs, largely funded by the public health system.⁵⁵ This involved considerable investment, the majority being domestic. It is estimated that the government contributes 2-3% of GDP to support AIDS prevention, care and treatment; this amount constitutes 80-90% of the required resources for treatment.⁵⁶ In 2004 Botswana introduced routine HIV/AIDS testing with all hospital visits. Additionally, Botswana participated in the African Comprehensive HIV/AIDS Partnerships (ACHAP), formed in 1999, which has continuously received funding. In 2010, a second national strategic framework for HIV/AIDS was put in place. Within its objectives, there are two specific to improving HIV treatment – to increase access to HIV/Tuberculosis/Sexual and

⁵⁴ The available data varies significantly from country to country. In particular, there is limited public data on access to medicines in some countries. For example, UNAIDS data for China and India.

⁵⁵ WHO (2014), "Country Cooperation Strategy – Botswana." Available at: http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_bwa_en.pdf. [Accessed on 08.03.2016].

⁵⁶ PEPFAR (2010), "Botswana partnership framework for HIV/AIDS 2010-2014: A collaborative effort between the government of Botswana and the government of the United States of America." Available at: <http://www.pepfar.gov/countries/frameworks/botswana/158545.htm>. [Accessed on 01.02.2016].

Reproductive Health across persons with HIV to 80% (in 2009, access was 63%) and to provide 90% of children and adolescents with HIV a package of HIV/AIDS treatment, care and support (in 2009, access was at 22%).

- In **Brazil**, a nationwide ART distribution programme was originally put in place by the Ministry of Health in 1986. It was then established as part of the Brazilian Constitution of 1988. In 1996, a federal law was introduced stating that all patients suffering from HIV/AIDS and in need of treatment should receive it free of charge. The main source of funding for Brazil's response to the HIV/AIDS epidemic was domestic; however, between 1993 and 2007 Brazil received three loans from the World Bank to strengthen its health system by training healthcare professionals, purchasing equipment and starting prevention campaigns.⁵⁷ In 2014, Brazil joined the UNAIDS 90-90-90 target by 2020, which aims to have 90% of people with HIV diagnosed, 90% of those diagnosed with HIV treated, and 90% of people with HIV virally suppressed (with an undetectable viral load). It is the first MIC to commit to providing ART to all people with HIV, regardless of CD4 cell count.⁵⁸
- **China** recognised that an HIV/AIDS epidemic would have significant consequences for economic well-being, quality of life and mortality. In 2003, China launched its first five-year action plan: 'Four Frees and One Care' policy providing access to free HIV testing, ART and prevention of HIV mother-to-child transmission. Subsequently, China has launched a number of "Five year action plans for the containment and prevention of HIV/AIDS". The most recent action plan was initiated in 2012. One of the main objectives is to "rapidly expand antiretroviral treatment to constantly increase accessibility and quality".⁵⁹ In China, domestic funds account for the largest majority of HIV/AIDS funding within the country.^{60,61}
- **India** has had an HIV/AIDS programme since the 1980s and created the National AIDS Control Organisation (NACO) in the early 1990s, which focused on preventive strategies.⁶² The implementation of a universal treatment programme for HIV/AIDS did not occur until 2004. That year, the government of India initiated a universal public ART programme, through which first-line ART were provided to the infected population at eight health centres in six of the highest prevalence states and the capital (by 2008, 137 centres in 31 states provided ART).⁶³ Towards the end of 2010, the Supreme Court of India ordered NACO to provide second-line treatment to the entire population, regardless of wealth or site of prior first-line treatment.⁶⁴ NACO has a budget of approximately \$2.6 billion, of which the majority is used for prevention efforts and only one-sixth for treatment. Funding comes from

57 Galvao et al. (2008), 'How the pandemic shapes the public health response — the case of HIV/AIDS in Brazil', Public Health Aspects of HIV/AIDS in Low and Middle Income Countries.

58 UNAIDS (2015), "15 by 15 – A global target achieved." Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_15by15_en.pdf. [Accessed on 16.11.2015].

59 UNAIDS (2015), "2015 China AIDS response progress report." Available at: http://www.unaids.org/sites/default/files/country/documents/CHN_narrative_report_2015.pdf. [Accessed on 16.11.2015].

60 Sun et al. (2010), 'Evolution of information-driven HIV/AIDS policies in China', International Journal of Epidemiology, 39:ii4–ii13.

61 Wu et al. (2010) 'China AIDS policy implementation: reversing the HIV/AIDS epidemic by 2015', International Journal of Epidemiology; 39:iii1–iii3.

62 AVERT (2011), 'Overview of HIV and AIDS in India,' accessible at <http://www.avert.org/AIDSIndia.htm>.

63 UNGASS (2010) 'Country Progress Report — India'. United Nations General Assembly Special Session (UNGASS).

64 Hindustan Times (2010), 'SC Cautions Government Over HIV Treatment' December 11.

a mixture of different origins, including the Indian government, international organisations such as the World Bank, and the Bill and Melinda Gates Foundation.⁶⁵ In 2012, India launched Phase IV of the National AIDS control programme which will run until 2017. In addition to other objectives, Phase IV seeks to increase the access to free first – and second-line ART through specialised ART healthcare centres.⁶⁶ However, most recently, we have seen a cut in the NACO budget such that from 2014 to 2016, there was a reduction in staff training for HIV voluntary counselling and testing.⁶⁷

- Early on, **Rwanda** recognised the need to address HIV/AIDS and created the national policy against HIV and AIDS (PNLS – La Politique nationale de lutte contre le SIDA) in 1987 and the National AIDS Control Commission (NACC/ CNLS) in 2000 to steer HIV/AIDS control activities.⁶⁸ Rwanda launched a Strategic Framework for HIV/AIDS Control (2002-2006) which aimed to improve the quality of care provision to HIV/AIDS infected and affected people by developing a supply network for ART (amongst other medical services) at national and provincial levels.⁶⁹ Meanwhile in 2004, the Government of Rwanda started purchasing HIV/AIDS drugs through the national tender procurement process (run by the Central Agency for the Purchasing of Essential drugs in Rwanda – CAMERWA). In 2009, after a range of analyses on the HIV epidemic, a National Strategic Plan (2009-2012) on HIV/ AIDS began with the intent to continually improve access to ART and services to progress towards universal access to HIV and AIDS services.⁷⁰ The Rwanda HIV and AIDS National Strategic Plan (2013-2018) continues with the same objective, specifically to extend ART coverage to 90% by 2018. To date, international funding for HIV/AIDS spending has been crucial as the public spending has been minimal (in 2012, 8.1% of all HIV/AIDS spending).⁷¹ The Government of Rwanda recognises the crucial role of external donor funding in the activities to control HIV/AIDS but also recognises the need to allocate domestic resources to strength the health system and finance HIV strategies. As such, the government has committed to increase the government budget allocated to health to 15% by 2017 (in 2011, this was 11.5%).⁷²
- There was a period of denial of HIV/AIDS from the 1980s during which there were no governmental programs to improve access to ARTs.⁷³ Eventually in 2003, the ‘Operational Plan for Comprehensive HIV and AIDS Care, Management and

65 Kaiser Family Foundation (2006), ‘India Primarily to Promote Condom Use in its HIV Prevention Programs, Health Minister Says’ September 5.

66 Department of AIDS Control, Ministry of Health & Family Welfare, Government of India “National AIDS Control Programme Phase-IV (2012-2017).” Available at: <http://www.naco.gov.in/upload/NACP%20-%20IV/NACP-IV%20Strategy%20Document%20.pdf>. [Accessed on 16.11.2015].

67 The Times of India (2016). “Budget cuts for NACO hits HIV/AIDS control programme” Available at: <http://timesofindia.indiatimes.com/city/visakhapatnam/Budget-cut-for-NACO-hits-HIV/AIDS-control-programme/article-show/52286050.cms>

68 CNLS /NACC (2002) “Strategic framework for HIV/AIDS control 2002-2006”. Available at: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_12_7589.pdf. [Accessed on 01.02.2016].

69 Ibid

70 CNLS (2009), “Rwanda national strategic plan on HIV and AIDS 2009-2012.” Available at: <http://apps.who.int/medicinedocs/documents/s18409en/s18409en.pdf>. [Accessed on 01.02.2016].

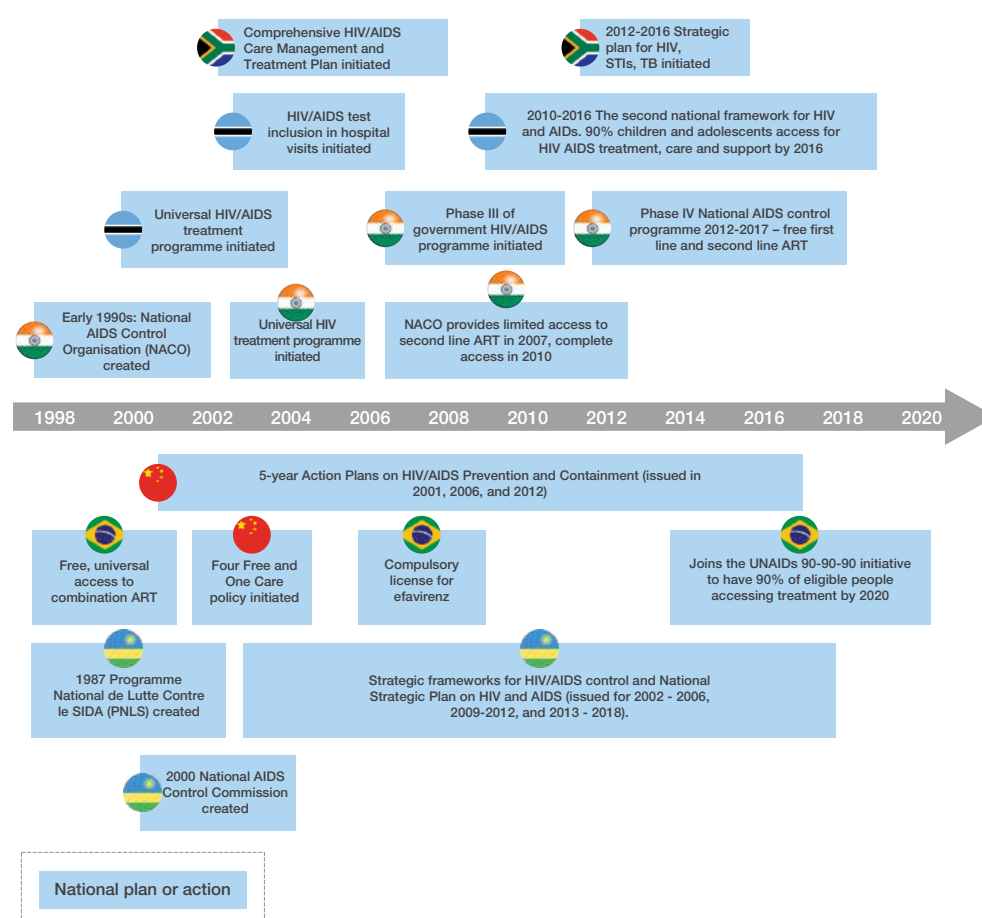
71 UNAIDS database (extracted from <http://www.aidsinfoonline.org/devinfo/libraries/asp/dataview.aspx>).

72 Republic of Rwanda Ministry of Health (2013) “Rwanda HIV and AIDS national strategic plan.” Available at: http://rbc.gov.rw/IMG/pdf/final_nsp_2013-2018.pdf. [Accessed on 01.02.2016].

73 Frontline (2006), “South Africa: The world’s largest AIDS epidemic.” Available at: <http://www.pbs.org/wgbh/pages/frontline/aids/countries/za.html>

Treatment for South Africa' was established and later launched in 2004.⁷⁴ This was the start of a detailed operation plan on antiretroviral treatment, setting out a comprehensive strategy on how to deal with the HIV/AIDS epidemic.⁷⁵ The new Comprehensive HIV/AIDS Care, Management and Treatment Plan included a provision for all patients attending public health facilities with a CD4+ count of under 200 cells/mm³ to receive ART.⁷⁶ 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 2009.⁷⁷ In 2012, South Africa launched a national strategic plan for HIV, Sexually Transmitted Infections, and Tuberculosis (2012-2016) with the objective of ensuring that at least 80% of people with HIV and eligible for treatment receive treatment (with at least 70% of these recipients being alive and still on treatment after five years).⁷⁸

Figure 9: Timeline of national strategies against HIV/AIDS in selected countries



Source: CRA analysis

74 Government of South Africa (2003), 'Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa', available at <http://www.info.gov.za/otherdocs/2003/AIDSplan/report.pdf>.

75 Wouters, et al (2010), 'Who is accessing public-sector anti-retroviral treatment in the Free State, South Africa? An exploratory study of the first three years of programme implementation', BioMed Central, 10, 387.

76 Johnson (2009) 'Access to Antiretroviral Treatment in Adults,' University of Cape Town.

77 CRA analysis using UNAIDS data repository.

78 South Africa Info (2012), "South Africa's HIV/AIDS battle plan". Available at: <http://www.southafrica.info/about/health/aids-prevention.htm#VkXK-HbhDcs#ixzz3rN47wmND>. [Accessed on 16.11.2015].

THE INTRODUCTION OF ART IN THE EDL

Looking at the our selected LIC and MIC countries, we found that HIV/AIDS drugs have been included in their Essential Drugs Lists (EDLs) since the very early stage of their design, including at least a molecule for each therapeutic class (Table 1). For all categories of ARTs, we find that the introduction of ARTs in national EDLs mimics the inclusion of ARTs in the WHO Essential Medicines List (EML). As such, the WHO EML seems to have had a positive influence on the introduction of ART in these countries.

Table 1: Year of introduction of molecules used for the treatment of HIV/AIDS in selected countries

	BOTSWANA	BRAZIL	INDIA	CHINA+	RWANDA	SOUTH AFRICA	WHO
NTRIs	2005	2000	2003	2005	2004	2006	1998
NNRTIs	2005	2002	2003	2005	2004	2006	2000
PIs	2005	2000	2003	2003	2004	2006	2000
Integrase Inhibitor	N/A	2012	N/A	N/A	N/A	N/A	N/A
Fusion and entry inhibitors	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fixed-dose combinations	2005	2002	2003	2005	2004	2006	2002

Source: CRA analysis of WHO Essential Medicines Lists and country specific EDLs. Note: *Indicates that the molecule was introduced but is not included in the 2012 EDL; +ARVs are not included on the Chinese EDL as Anti-AIDS medicines are provided by the government for free to treat HIV/AIDS, the year reflect the introduction of the class within the 'Four Free and One Care' program

Though China does not include ART on its EDL, through the Chinese 'Four Free and One Care' policy, in 2005 (two years after the introduction of the policy), China's first-line regimen followed the WHO guideline, comprising zidovudine or stavudine + lamivudine or didanosine + nevirapine or efavirenz (two NTRIs and one NNRTI).^{79,80} Limited amounts of combinations of zidovudine + lamivudine and of efavirenz are also available.⁸¹

THE EXISTING EVIDENCE ON ACCESS TO HIV/AIDS TREATMENTS IN LICs AND MICs

International organisations such as UNAIDS and WHO, as well as academic researchers, have developed studies or surveys to determine the extent to which ART are used for the treatment of HIV/AIDS within LICs and MICs. As described above, in order to control HIV/AIDS, countries began launching national strategies based on prevention mechanisms and enhancing treatment options. Here we discuss access of ART in LICs and MICs and then more specifically in the selected countries in this analysis.

79 Zhang et al. (2005), 'Current progress of China's free ART program', Cell Research, 15, 877-882

80 Xing et al. (2013), 'HIV Drug Resistance and Its Impact on Antiretroviral Therapy in Chinese HIV-Infected Patients', PLOS ONE, 8, 2.

81 WHO (2005), 'Summary country profile for HIV/AIDS treatment scale-up', WHO publication.

Access to ART within LICs and MICs

The most widely used measure of access is the ART coverage rate; it is the indicator recommended by the United Nations General Assembly Special Session on HIV/AIDS (UNGASS). Coverage is determined by the fraction of people eligible for ART who receive effective treatment. This provides 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 antiretroviral drugs; however, due to different tolerability profiles, or perhaps due to the development of resistance, HIV/AIDS patients may need to receive specific combinations. The wrong combination of antiretroviral drugs can have significant consequences for patients, for example, by accelerating resistance.
- Until very recently the WHO recommended HIV/AIDS patients treatment eligibility assessment based primarily on CD4 cell count. The threshold below which ART should be initiated is established by treatment guidelines (which have recently been updated again). The immediate consequence of the change to treatment recommendations has been an increase in the number of people eligible for ART, and subsequently coverage rates (compared to reported figures in previous years) have fallen. Now that the WHO have extended treatment eligibility to all CD4 counts, the definition of coverage could be less varied in the future (although national eligibility criteria will inevitably still vary).
- 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 of 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 necessary to minimise the likelihood of patients developing resistance to treatments. ART coverage rates do not take into account adequate monitoring and support of patients receiving ART as a component of effective access.

In this report, we refer to the percentage of people currently receiving ART among all people with HIV (UNAIDS and WHO definition). The numerator is all people receiving ART according to national or international treatment eligibility criteria and the denominator is all people with HIV in order to ensure that the data is comparable across countries (this takes into account that the national criteria for ART eligibility varies across countries).^{82,83}

Since 2003, the number of people with access to ARTs in LICs and MICs has rapidly increased from a mere 400,000 to 11.7 million at the end of 2013.⁸⁴ This means that

82 WHO and UNAIDS (2015), "Global AIDS response progress reporting – 2015". Available at: http://www.unaids.org/sites/default/files/media_asset/JC2702_GARPR2015guidelines_en.pdf. [Accessed on 02.02.2016].

83 WHO (2015). "Estimated antiretroviral therapy coverage among people living with HIV(%)." Available at: http://apps.who.int/gho/indicatorregistry/App_Main/view_indicator.aspx?iid=4477. Accessed on 02.02.2016].

84 WHO (2013), "Antiretroviral therapy coverage among all age groups." Available at: http://www.who.int/gho/hiv/epidemic_response/ART_text/en/. [Accessed on 01.02.2016].

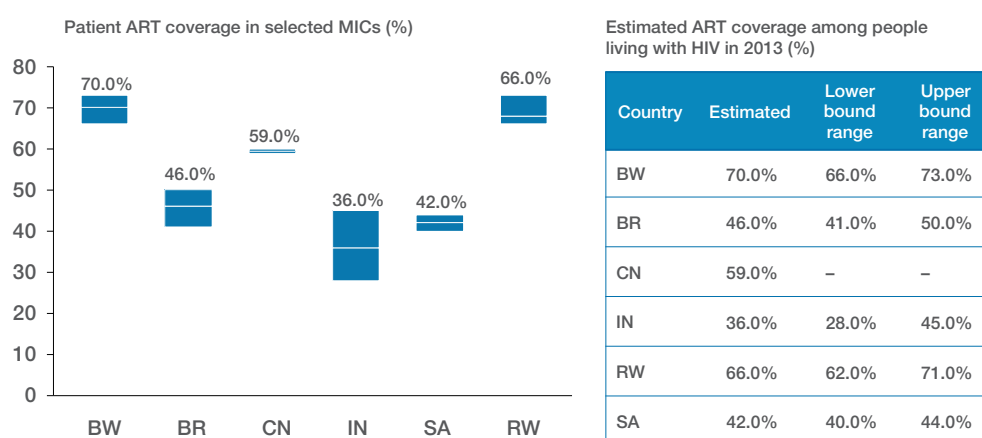
all LICs and MICs⁸⁵ had substantially improved the access to ART with ART coverage increasing from 20% to 30%.⁸⁶ While this represents significant progress, according to the new 2013 WHO guidelines for HIV/AIDS treatment, which widens ART eligibility, a remaining 64% of patients eligible for ART in LICs and MICs still lack ART access.⁸⁷ This suggests that there is substantial progress to be made to achieve the UNAIDS target to treat 90% of all people diagnosed with HIV by 2020.⁸⁸

Access to ART within selected countries

When we combine the WHO and UNAIDS data available, we can see that the introduction of the national policies previously described has contributed significantly to the increase in access to ART in the selected LICs and MICs. Every country has seen a large rise in the population receiving treatment, and in all countries this continues to grow significantly year on year.

In the selected countries, Botswana and Rwanda had the highest patient ART coverage in 2013 (70% and 66%). In the same year, Brazil and South Africa had coverage rates slightly below 50% while India had the lowest coverage rate, at 36%. There was no 2013 data for China available in the WHO Global Health Observatory Data Repository. However, according to a UNAIDS report, the estimated coverage percentage was 59% in 2013.⁸⁹ Figure 10 illustrates the level of coverage in the selected countries.

Figure 10: Use of medication in patients with HIV/AIDS by country, with upper and lower bounds, 2013



Notes: Botswana (BW), Brazil (BR), China (CN), India (IN), Rwanda (RW), South Africa (SA); + Percentage for China taken from UNAIDS (2015), “2015 China AIDS response progress report.” which did not provide lower and upper bound ranges. Source: WHO Global Health Observatory Data Repository, accessed February 2016

⁸⁵ We analysed 83 countries with data availability on UNAIDS data repository

⁸⁶ CRA analysis based on UNAIDS data repository. Note: Various countries lack data.

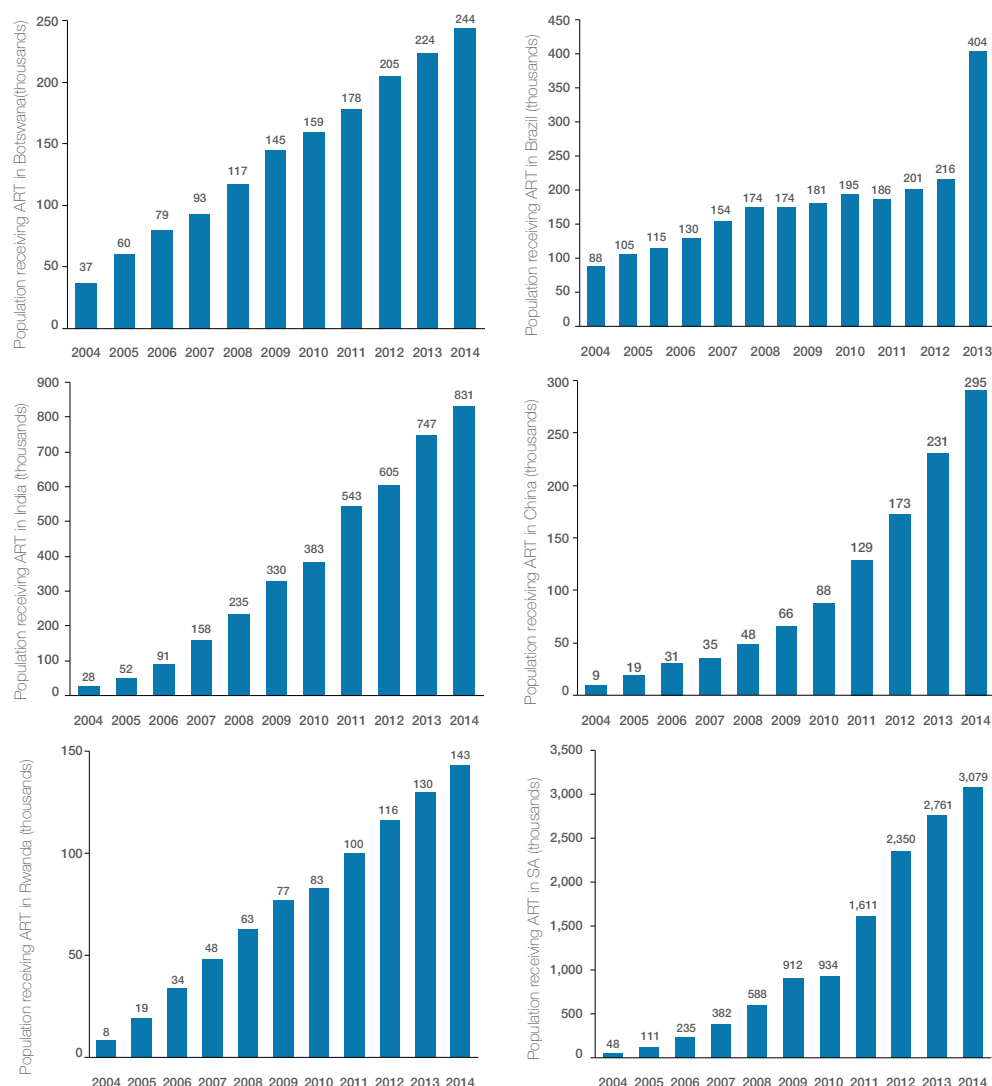
⁸⁷ The change in the threshold, which now recommends ART to be initiated at an earlier stage of disease, increased the number of eligible patients in low – and middle-income countries by 45%, from 10.1 million to 14.6 million. In spite of continued progress, according to the new guidelines only 36% of patients in need of ART’s in low – and middle-income countries currently have access to it. We recognise that the 2015 WHO guidelines extends ART eligibility to all people with HIV CD4 counts. But, there is no data availability yet to assess coverage based on 2015 WHO guidelines. Available at: http://www.who.int/gho/hiv/epidemic_response/ART_text/en/

⁸⁸ UNAIDS (2014), “90-90-90 An ambitious treatment target to help end the AIDS epidemic.” Available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. [Accessed on 01.02.2016].

⁸⁹ UNAIDS (2015), “2015 China AIDS response progress report.” Available at: http://www.unaids.org/sites/default/files/country/documents/CHN_narrative_report_2015.pdf. [Accessed on 16.11.2015].

When we looked at time series data on the population receiving ART, we found that access to ART has improved significantly across all the selected countries. This is shown in Figure 11.

Figure 11: Uptake of ART (thousands) in the selected countries



Notes: There was no data from UNAIDS data repository for Brazil 2012-2014 and hence data may not be consistent or for Rwanda 2004-2010. Hence, reference was made to Brazil Communication Advisory, Department of STDs, AIDS, and Viral Hepatitis report on 90-90-90 target for 2013 data. Rwanda 2004-2010 data referred to (Treatment and Research AIDS Centre of Rwanda) Source: CRA Analysis using UNAIDS data repository, accessed February 2016

Access to FDC

Data looking at the level of uptake of FDC across the selected countries is scarce. However, as shown in Table 1, all countries have included FDC in their EDL. South Africa is an exception as the FDC available since 2006 was a ritonavir-boosted PI rather than a combination of different ART. The provision of other FDC products began in 2013, when there were regulatory changes in the country.^{90,91}

90 SA news, "SA making progress in tackling HIV – Motlanthe" Available at: <http://www.sanews.gov.za/south-africa/sa-making-progress-tackling-hiv-%E2%80%93-motlanthe>. [Accessed 16.11.2015].

91 SA news, "SA begins single-dose HIV drug roll-out." Available at: <http://www.southafrica.info/services/health/hiv-080413.htm#VkntuXbhDcs>. [Accessed 16.11.2015].

It is important to recognise that variations in access to ARVs within a country's population remain. Looking at our case study countries, paediatric access to ART is a particularly challenging in Brazil, China and India due to the lack of paediatric specialists and the lack of paediatric formulations.^{92,93,94} In India and Botswana, it remains the case that fewer women have access to ARVs in comparison to men.^{95,96} There is also recognition of challenges in accessing ARVs in rural areas such as the Amazon in Brazil.⁹⁷ But while such variation in access to ARVs remain, we find over the years, there have been improvements in access. For example, one study found that in India, the average travel distance for a patient to access ARV reduced from 70km to 30km since 2007 and this has increased the level of ARV access for HIV/AIDS patients in rural settings.⁹⁸

Factors affecting access

We have also examined the factors that contribute to the improvements in access to ART. In particular, we have conducted a statistical analysis to understand the determinants of access over the last decade. Drawing on this analysis and the experience of the case studies, our conclusions regarding the factors determining access are:

- The date when the universal ART 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. It is notable that even after many years, the period of initiation remains an important factor. This is consistent with countries updating and refreshing their national policies over time and the on-going importance of prioritisation.
- 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

92 The Body (2009). "Many Chinese Children living with HIV do not have treatment access". Available at: <http://www.thebody.com/content/art51368.html> [Accessed 16.05.2016]

93 Infochange. "India launches national paediatric HIV/AIDS". Available at: <http://infochangeindia.org/public-health/news/india-launches-national-paediatric-hiv-aids-initiative.html> [Accessed 16.05.2016].

94 Mothi, S.N. et al (2011). Paediatric HIV – trends and challenges. Indian J Med Res 134; pp 912-919. Available at: <http://icmr.nic.in/ijmr/2011/december/1214.pdf>. [Accessed 16.05.2016].

95 AVERT (2013). "HIV and AIDS in Botswana" Available at: <http://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/botswana>. [Accessed 16.05.2016]

96 MindText (2010). "Impact of HIV/AIDS on the Indian economy". Available at: http://www.mindtext.org/view/86/Impact_of_HIV/AIDS_on_the_Indian_economy/. [Accessed 16.05.2016]

97 Brazilian Ministry of Health (2014) "Global AIDS Responses Progress Report". Available at: http://www.unaids.org/sites/default/files/en/dataanalysis/knowyourresponse/countryprogressreports/2014countries/BRA_narrative_report_2014.pdf. [Accessed 16.05.2016]

98 Fahim, S (2012). "Decentralizing treatment services with link ART centres – experience from Karnataka, South India" *Retrovirology* 9; p82

rate, being instead forced to raise access more gradually over time. There is little doubt that by improving education and reducing stigma countries, in particular India and Botswana, can reduce some of the major barriers that exist for female and paediatric patients to seek out voluntary testing and treatment, which is critical for reducing the time to diagnosis and initiating effective treatment regimens.⁹⁹

- The substantial increase in resources from the international community that has been dedicated to promoting health over the last several years has changed 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. MICs have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit. Hence, it is not surprising that international funding means that the characteristics of low-income countries are less important in determining access.
- The innovative industry has contributed to the affordability of ART. There are many examples of industry partnering with international organisations and national governments. For example, the Accelerated Access Initiative¹⁰⁰, established in 2000 to increase the affordability of HIV/AIDS treatment in developing nations and middle income countries. The African Comprehensive HIV/AIDS partnership or ACHAP¹⁰¹ saw a donation of HIV/AIDS treatment to Botswana for a duration of five years.¹⁰² Moreover, voluntary licensing has emerged as a common practice since the beginning of the 21st century. As Figure 12 illustrates below, in comparison to compulsory licensing, for which examples are few, there is an increasing trend in the number of products voluntarily licensed by the innovative manufacturer to generic companies.^{103,104} We recognise that while the threat of compulsory licensing may have played some role in price negotiations with pharmaceutical companies, there have been a few cases of compulsory licensing and many more examples of voluntary licensing. Facilitated by the Medicines Patent Pool (MPP)¹⁰⁵, pharmaceutical companies have licensed their products voluntarily to producers in third countries, allowing them to supply generic versions of the licensed products only in low-income and some middle income countries.¹⁰⁶ This continues to be important. Most recently, two novel products – dolutegravir and a fixed dose

99 AVERT (2013). "HIV and AIDS in Botswana". Available at: <http://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/botswana>. [Accessed 16.05.2016].

100 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.

101 This was a partnership between the Government of Botswana, The Merck Company Foundation and the Bill & Melinda Gates Foundation.

102 Sturchio, J (2004), "Partnership for action: the experience of the Accelerating Access Initiative, 2000-2004, and lessons learned." Available at: http://www.who.int/hiv/amds/AAI_chapter6.pdf

103 MPP (2016), "Target medicines – products already licensed to the MPP". Available at: <http://www.medicinespatentpool.org/ourwork/target-medicines/>. [Accessed on 08.03.2016].

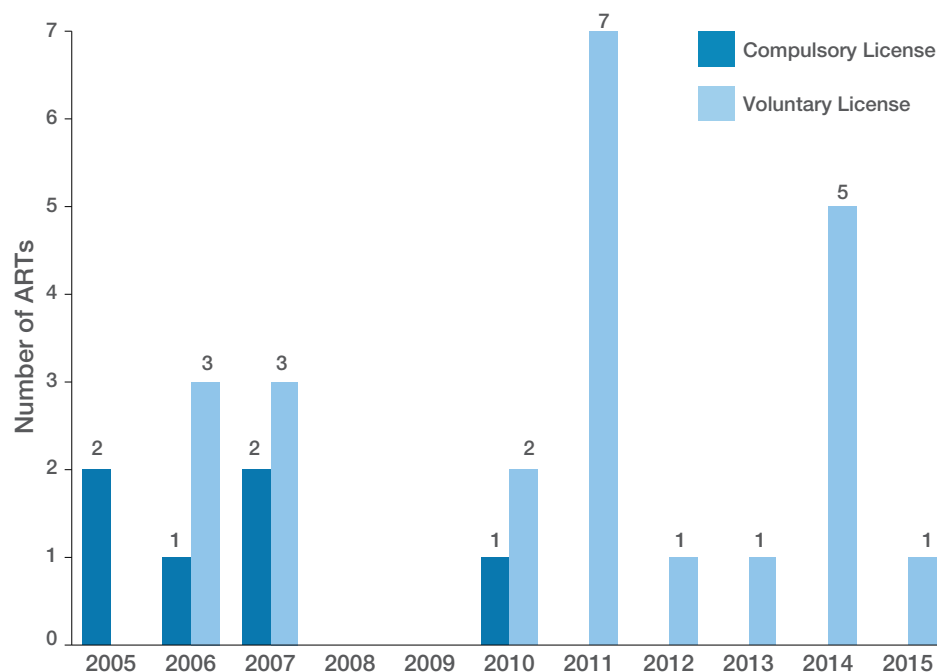
104 WHO (2014), "Innovation and access to medicines: case study for HIV /AIDS and Hepatitis C: Trends in voluntary licensing." Available at: http://www.wipo.int/meetings/en/doc_details.jsp?doc_id=292236. [Accessed on 08.03.2016].

105 The MPP is a United Nations backed organisation that partners with the industry to provide generic manufacturing licenses for HIV treatment (also viral hepatitis C and tuberculosis).

106 The following link provides an overview of the industry's approach to voluntary licencing and non-assertion: http://www.ifpma.org/fileadmin/content/Innovation/IP%20and%20Access/20100728_Statement_VoluntaryLicensing_NonAssert_28July10.pdf

combination product of elvitegravir + cobicistat tenofovir+ emtricitabine were voluntarily licensed through the MPP to a range of countries in need, such as the least developed countries, Sub Saharan African countries and lower MICs.^{107,108} As Figure 12 illustrates below, in comparison to compulsory licensing, for which examples are few, there is an increasing trend in the number of products voluntarily licensed by the innovative manufacturer to generic companies.

Figure 12: Number of products with compulsory and voluntary licenses 2005-2015



Notes: The large number of ARTs in 2011 reflects the creation of the Medicines Patent Pool in 2010. Sources: MPP 2016, WHO 2014

This has benefited all of the case studies examined. This has been, for instance, the case with a number of Indian generic companies that currently supply a considerable share of ART consumed in low-income countries, especially sub-Saharan Africa.¹⁰⁹ This has meant that sub-Saharan Africa countries like Rwanda and South Africa are able to supply a large proportion of first line ARTs with generic alternatives (65%).¹¹⁰ Each country has its own position regarding their access to differential pricing schemes depending on their income level and the state of their epidemic. Botswana and South Africa also generally have access to the lowest prices because they are sub-Saharan African countries with large epidemics. Middle-income countries with concentrated epidemics; hence they do not usually have access to the same pricing arrangements as the countries named above. For example, in 2013, the annual price of second-line ART per patient in China (\$740) was higher than that of South Africa (\$204).¹¹¹

107 GSK (2016), "ViiV healthcare extends MPP license agreement for dolutegravir to cover all lower middle income countries." Available at: <http://www.gsk.com/en-gb/media/press-releases/2016/viiv-healthcare-extends-medicines-patent-pool-licence-agreement-for-dolutegravir-to-cover-all-lower-middle-income-countries/>

108 MPP (2015), "Second amended and restated license agreement with Gilead Sciences." Available at: <http://www.medicinespatentpool.org/wp-content/uploads/MPP-Gilead-Sciences-Amended-Licence.pdf>

109 Chien (2007), "HIV/AIDS Drugs for sub Saharan Africa: How do brand and generic supply compare?" PLoS One, 2(3).

110 Between 2004 and 2006, the total percentage of first line ARVs procured = 65% generic, 35% branded. Chien, C (2007), "HIV/AIDS drugs for sub-Saharan Africa: How do brand and generic supply compare." Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1805689/>

111 MSF (2014), "Untangling the web of antiretroviral price reductions." Available at: https://www.msfaccess.org/sites/default/files/MSF_UTW_17th_Edition_4_b.pdf. [Accessed on 08.03.2016].

- Generic manufacturers have been important in all of the case studies. However, this varies significantly from country to country. In Brazil, 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.
- Looking at the patent landscape for first line ART recommended by the WHO 2010 guideline, we observe for the vast majority of products the patent have expired in our selected LIC and MICS but some secondary patents (for the ART, including combinations) remain.^{112,113} To understand the role of patent we considered whether the use of compulsory licensing or provision of generics through using Paragraph 6 have played a significant part in improving access. Very few products have been compulsory licensed (and even fewer have used Paragraph 6 provisions). In particular, across our selected countries, only Brazil has used it once.¹¹⁴ We do not find this is an important factor explaining access. 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.

2.3. THE VALUE OF MEDICINES FOR HIV/AIDS

We find that there is considerable existing evidence on the value that ART have brought within LICs and MICs and in particular within the selected countries.

THERAPEUTIC/CLINICAL BENEFITS

The mortality rates associated with HIV/AIDS have decreased within all the selected countries. As shown in Figure 13, all countries have seen a reduction in the number of deaths due to HIV/AIDS from 2002 to 2008. While India has the largest absolute reduction in the total number of deaths, the largest percentage reduction is in Botswana.

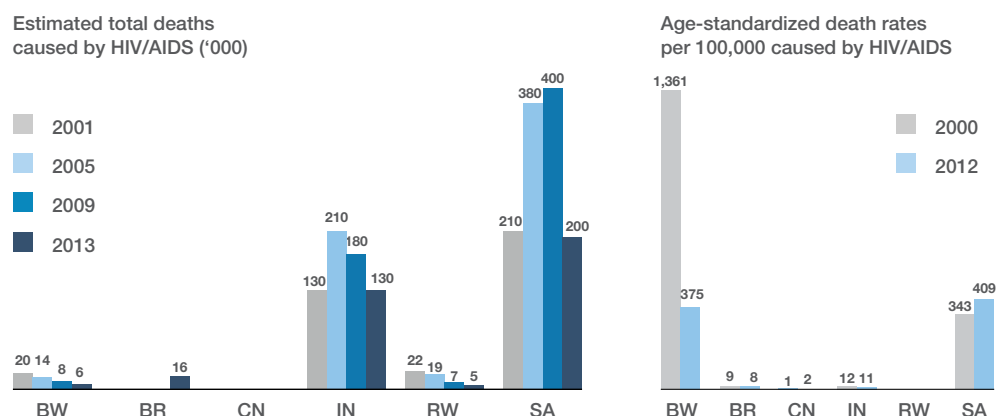
As HIV/AIDS has transitioned to a more chronic disease, it is possible that the number of DALYs could increase even if mortality has decreased. However, DALYs also show a general decrease throughout the countries.

112 WHO (2014) "Increasing access to HIV treatment in middle-income countries – Key data on prices, regulatory status, tariffs and the intellectual property situation." Available at: http://www.who.int/phi/publications/WHO_Increasing_access_to_HIV_treatment.pdf. [Accessed on 02.02.2016].

113 Intellectual property could be a larger issues for second line ART. At present, the vast majority of HIV patients on treatment are on first line ART, most of which are off – patent and the proportion of patients on second line treatment in resource limited settings are as low as 1-5%. Patrikar, S et al (2015) "Profile of HIV patients on second line antiretroviral therapy: the Indian experience." Available at: <http://www.omicsonline.org/open-access/profile-of-hiv-patients-on-second-line-antiretroviral-therapy-the-indian-experience-2155-6113-1000459.php?aid=53428>. [Accessed on 02.02.2016].

114 WHO (2014). "Increasing access to HIV treatment in middle-income countries – Key data on prices, regulatory status, tariffs and the intellectual property situation; Medicines Patent Pool". Available at: <http://www.medicinespatentpool.org/mpp-licence-on-tenofovir-disoproxil-fumarate-tdf/>. [Accessed on 02.02.2016].

Figure 13: Burden of HIV/AIDS within selected LICs and MICs



Notes: Botswana (BW) Brazil (BR), India (IN), China (CH), South Africa (SA); limited data for China and Brazil in WHO Global Health Observatory Data Repository; In China, we see the age standardized mortality increased from 1.1 to 2.4 this is reflective of the fact that an increased number of people with HIV are being diagnosed. Source: CRA analysis using WHO Statistical Information System (WHOSIS), Global burden of disease. Available here http://www.who.int/healthinfo/global_burden_disease/gbd/en/index.html, accessed February 2016

The reduction of the burden of HIV/AIDS within these markets is aligned with an improvement in access to ART. The relation between the use of ART and the reduction of the burden of disease has been demonstrated in literature:

- In Brazil, the World Bank stated that due to changes in policy that promoted both prevention and access to innovative treatment, between 1997-2003, there were over 360,000 hospitalisations avoided (representing a 85%) reduction in relation to the affected population in the early 1990s.¹¹⁵
- In India, the National Institute of Medical Statistics and the National AIDS Control Organization found that wider access to ART through the scale-up of free ART since 2004 has saved 150,000 lives by 2012. Over the next five years (until 2017), it is further estimated that around 50,000 to 60,000 deaths will be averted annually.¹¹⁶
- In Rwanda, the Ministry of Health estimated that the impact of following WHO revised guidelines on the use of ART for HIV (2013) would increase the number of people that need ART to 26 million people (up from 17 million according to old guidelines). As such, the Ministry of Health estimated that this would avert close to 2 million infections and 1 million deaths in the next decade.¹¹⁷
- In South Africa, a study conducted by Granich et al. (2012) demonstrated that there are almost instantaneous benefits to an expansion in ART coverage such as the one outlined in the WHO 2010 guidelines, compared with WHO 2006 guidelines.¹¹⁸ The study models the estimated new HIV/AIDS infections, deaths,

115 Greco D, Simao M (2007) 'Brazilian policy of universal access to AIDS treatment: sustainability challenges and perspectives', WHO report.

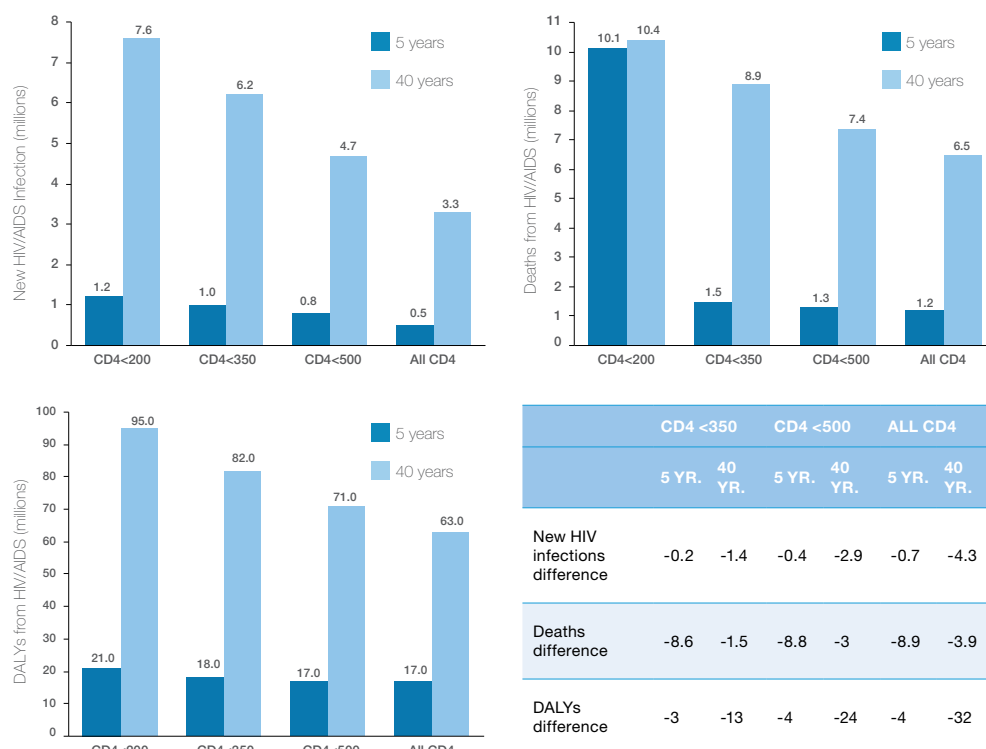
116 National Institute of Medical Statistics and National AIDS control organisation (2012), "Technical Report - India HIV estimates-2012". Available at: <http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/data-and-analysis/tools/spectrum/India2012report.pdf>. [Accessed on 16.11.2015].

117 Republic of Rwanda Ministry of Health (2013). "Rwanda receives new QARV treatment guidelines." Available at: http://www.moh.gov.rw/index.php?id=34&tx_ttnews%5Btt_news%5D=27&cHash=3f61c3a4e3f3cfc76084e2c3eb9b5b. [Accessed on 01.02.2016].

118 Expansion from CD4+ <200 cells/mm³ (WHO 2006).

and DALYs lost for several different coverage scenarios. The authors show that if HIV/AIDS patients with any CD4 amount are placed on ART immediately, rather than after exhibiting a specific CD4 cell amount, after just 5 years there would be 700,000 fewer new infections than if the 2006 WHO guidelines were being practiced. There would also be significantly fewer deaths, with 8.9 million more people surviving the following 5 years and a reduction in DALYs lost of 4 million. This is summarised in Figure 14 with the total difference between the highest coverage scenario and the baseline scenario.¹¹⁹

Figure 14: Therapeutic and clinical benefits of increasing ART coverage criteria in South Africa



Source: Granich R et al. (2012) Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050, PLOS ONE, Vol. 7, no. 2. Note: All CD4 levels scenario involves offering ART to everyone immediately after diagnosis with HIV irrespective of CD4 count

- Zhu et al (2013) assessed the National Free Antiretroviral Treatment Program (NFATP) in China and also showed how mortality rates in HIV patients fell sharply among people receiving antiretroviral therapy between 2003 and 2009. Overall, people were about 30% less likely to die in the period 2008-09 compared to 2003-04, before the program expanded.¹²⁰ These findings are consistent with a 2015 study by Huang et al that studied a cohort of adult HIV patients in Shenzhen from 2003 to 2014. Of the 6,897 patients followed up, 44.92% received ART. In the regression analysis, those receiving ART during the study had a lower presence of tuberculosis and lower mortality rate.¹²¹

119 Granich R et al. (2012) 'Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050', PLOS ONE, 7, 2.

120 Zhu et al (2013), 'Decreasing excess mortality of HIV-infected patients initiating antiretroviral therapy: comparison with mortality in general population in China, 2003-2009', Journal of Acquired Immune Deficiency Syndromes, 10.

121 Huang, P et al (2015). "Long-term effectiveness of antiretroviral therapy in China: an observational cohort study from 2003-2014". Int. J. Environ. Res. Public Health vol.12 pp.8762-8772. Available at: doi: 10.3390/ijerph120808762. [Accessed 13.11.2015].

In addition, the benefit of ART is increasingly viewed in the context of preventing HIV transmission rather than that of treatment alone. ART plays a crucial role in the prevention of mother to-child transmission (PMTCT). 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 PMTCT ART. In some countries like South Africa, coverage for PMTCT has reached 90%, which has drastically reduced the transmission to children from a peak of over 200,000 in 2004 to fewer than 100,000 in 2011.^{122,123}

We searched for studies on the value of supplying the population with FDC in the selected countries, but these are limited. A WHO meeting report stated that there is indeed little reliable evidence on the value of FDC in terms of adherence (or treatment outcomes) in HIV/AIDS.¹²⁴ Although there were articles that speculated that the relative ease of use of such medicines would improve adherence to ART, we have found little empirical evidence of this.

However, studies in high income countries have demonstrated the value of FDC in terms of patient adherence. A team studied the differences in adherence between patients using FDC and separate combinations in the US using a large health insurance claims database.¹²⁵ Patients using FDC had a higher adherence to the medicines than those taking the drugs separately. It is reasonable to assume that if FDC can improve adherence in a high income country like the US, the benefits would also be mirrored in LICs and MICs, where adherence is reportedly similar for ART.¹²⁶

Although we did not find evidence on the selected countries, this is also supported by a study in Uganda that concluded that patients with HIV/AIDS purchasing generic FDC have higher rates of adherence, which brings clinical benefits.¹²⁷ As previously mentioned, South Africa has recently introduced policies to provide access to FDC. Although there is no evidence on its success yet, the move is welcomed by the South African National AIDS Council (SANAC), who are optimistic that it will encourage a higher rate of adherence as well as simplifying prescribing, dispensing and monitoring for nurses and pharmacists, and also simplifying procurement and supply chain management.^{128,129}

CONTROLLING COSTS IN THE HEALTHCARE SYSTEM

Next we considered if there was evidence that improving therapeutic and clinical aspects can have positive repercussions on the costs incurred by the healthcare system. If patient hospitalisations can be reduced due to new treatment options, the costs incurred within the healthcare system will also be reduced, as fewer resources will be

122 CRA (2011), 'Evidence on access to Essential Medicines for the treatment of HIV/AIDS', a report commissioned for IFPMA.

123 CRA analysis using UNAIDS data repository.

124 WHO, (2003) 'Fixed-Dose Combinations for HIV/AIDS, Tuberculosis, And Malaria', Report of a meeting held 16-18 December 2003, Geneva.

125 Valenti W (2004), 'Expanding Role of Coformulations in the Treatment of HIV Infection: Impact of Fixed-Dose Combinations', Medscape news, 14, (10).

126 Red A, and Biadgilign S (2012), 'Determinants of Adherence to Antiretroviral Therapy among HIV-Infected Patients in Africa', AIDS Research and Treatment.

127 Oyugi J et al. (2007), 'Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda', PubMed, vol. 21, iss. 8, 965 971.

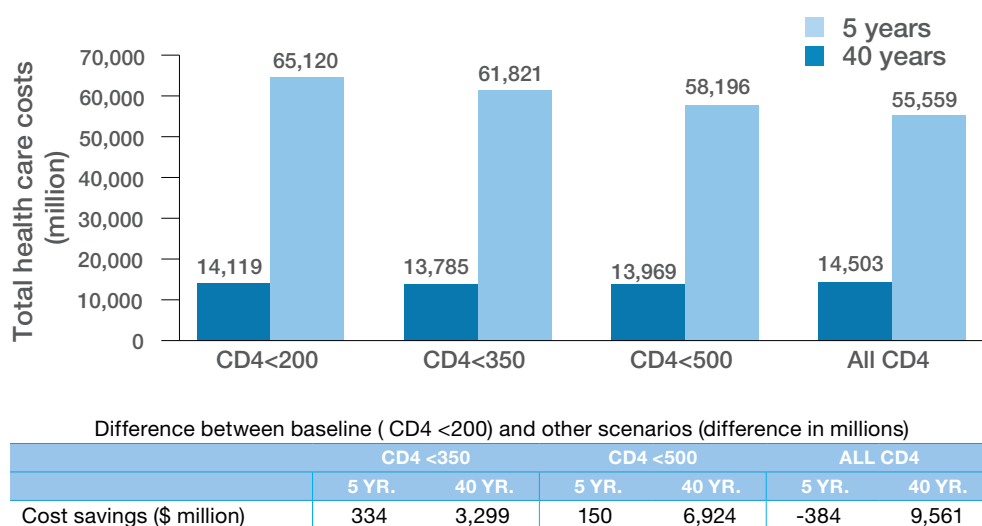
128 SA news (2013), 'SANAC welcomes fixed dose combination ARVs', seen on SAnews.gov.za.

129 South Africa.info (2012), 'Single-dose HIV drug welcomed', seen on SouthAfrica.info.

consumed. Several studies have assessed the effect of treatment on the overall health-care costs, proving that access to ART leads to a reduction in healthcare costs.

- In Brazil, for example, it is estimated that through the universal provision of ART to patients suffering from HIV/AIDS in 2002, the Brazilian government averted over 60,000 AIDS cases, 90,000 deaths and almost 360,000 AIDS-related hospital admissions, contributing to overall healthcare savings of over \$200 million.¹³⁰ Additionally, WHO data from Brazil demonstrates that providing universal access to ART was cost-effective to the Brazilian government as the estimated cost of providing ART between 1996 and 2002 was approximately US\$1.8 billion, whereas savings achieved through reducing both hospital and ambulatory care services were \$2.2 billion.¹³¹
- In South Africa, a team developed a model that projected the benefits of incremental increases in the coverage of HIV/AIDS. The model found that increases in coverage would lead to significant downstream financial savings. The study, conducted by Granich *et al.* (2012), demonstrated the benefits with regards to the total cost of HIV/AIDS care, and modelled the potential savings that extending the treatment eligibility criteria could enable (cost and savings listed in Figure 15). The study compares different eligibility criteria for ART usage, demonstrating how criteria that widens treatment for a larger population delivers significant benefits. The study reports that if all patients diagnosed were treated immediately with ART, overall costs of HIV care would decrease by \$10 billion over a 40-year period, and the breakeven point would be reached by 2023.

Figure 15: Economic effects of extending the ART eligibility criteria in South Africa



Source: Granich R et al. (2012) Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050, PLOS ONE, Vol. 7, no. 2. Note: All CD4 levels scenario involves offering ART to everyone immediately after diagnosis with HIV irrespective of CD4 count

130 Teixeira et al. (2004), 'The Brazilian Experience in Providing Universal Access to Antiretroviral Therapy', Le Publieur, available at <http://www.lepublieur.com/anrs/ecoAIDS6.pdf>.

131 IRIN Web special (2005), 'Lazarus drug - ARVs in the treatment era', available at <http://www.irinnews.org/pdf/in-depth/ARV-era.pdf>; Granich et al. (2012), 'Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050', PLOS ONE, 7, 2.

- A similar cost-benefit model on ART provision was created by Meyer-Rath et al (2015) for a mining workforce in South Africa (the Workplace Impact Model). Using data on care utilisation and absenteeism, the model found that when compared to a scenario of no treatment provision, ART provision is associated with cost savings. When ART were provided, the annual cost of HIV to the company decreased by 5% and this meant cost per HIV-positive employee decreased by 14% by 2022. At a national level, the model estimated an average saving of USD \$950,000 per year with 80% of these savings attributed to reductions in benefit payments and inpatient care costs.¹³²

WIDER BENEFITS TO SOCIETY

As with all severe diseases, in addition to the impact directly on patients there is concern over the impact HIV/AIDS has on economic activity, for example due to productivity losses. In South Africa, for example, evidence suggests that HIV/AIDS raises the cost of labour and also diminishes the competitiveness of African businesses in the global marketplace.¹³³ Indeed, looking at the case of the mining company in South Africa it is estimated that HIV/AIDS can add an additional 4-5% to company costs.¹³⁴

A number of studies have examined the impact of ARTs on businesses, mainly through the reduction of absenteeism:

- In Botswana, a study analysed data on work absenteeism, comparing patients enrolled in one of Africa's first ART programmes and unaffected workers. The study finds evidence that patients suffering from HIV/AIDS display similar absenteeism patterns as unaffected workers until one year prior to the start of the treatment. At this point, absenteeism among HIV/AIDS patients increases to a peak of 5 days in the month of treatment onset. Within one year of the programme, the HIV/AIDS patients begin to recover, and for the following few years demonstrate similar patterns to unaffected workers. The authors conclude that ART are effective in the short, medium and long run with regards to improving both the health and productivity of working patients suffering from HIV/AIDS.¹³⁵
- In India, the impact of ART on socio-economic outcomes was examined using the Tamil Nadu Family Care Continuum program in India. Six months after ART initiation, the patients' participation in the labour force had increased by 26% and the weekly work hours had increased by an average of 14.5 hours.¹³⁶ The same authors conducted a longer two-year study on 1,238 HIV infected patients between 2005 and 2007. It observed that ART initiation was associated with 5.5 additional working hours per week at the 6-month examination point and at 24 months after ART initiation, patients' employment levels were double that of baseline.¹³⁷

132 Meyer-Rath, G et al (2015) "The impact of company - level ART provision to a mining workforce in South Africa: A cost-benefit analysis". Available at: <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001869>. [Accessed 13.11.2015].

133 Rosen et al. (2004), 'The cost of HIV/AIDS to business in SA', Official Journal of the International AIDS Society, 18, 2.

134 Du Plessis and Venter (2010), 'HIV/AIDS Is An Epidemic: Empirical Assessment Of The State Of Affairs In A Developing Country', International Review of Business Research Paper, 6, 2.

135 Habyarimana et al. (2009), 'HIV/AIDS, ARV Treatment and Worker Absenteeism: Evidence from a Large African Firm', available at <http://www.columbia.edu/~cp2124/papers/arv.pdf>.

136 Thirumurthy et al. (2008), 'The impact of antiretroviral therapy on socio-economic outcomes of HIV-infected patients in Tamil Nadu Family Care Continuum program (TNFCC), India', XVII International AIDS Conference.

137 Thirumurthy, H et al (2011), "Two-year impact on employment and income among adults receiving antiretroviral therapy in Tamil Nadu, India: a cohort study." AIDS Vol 25, Issue 2 pp. 239-246.

- In South Africa, the experience of a South African employer-based HIV/AIDS care programme was examined. The analysis found that the short-term savings exceeded costs across all models of employer-based ART provision. The study demonstrated that 2 years after implementation, the net cost per employee decreased from \$220 per patient/month to \$170 per patient/month. Absenteeism decreased from 7.5 days to 2.9, 2.2 and 2.1 days per month (after 6, 12, and 18 months respectively).¹³⁸ The benefit in productivity from ART was also examined in a study by Rosen et al (2014), which looked at 879 South African HIV/AIDS patients of public or non-governmental clinics and followed these patients for a maximum of 5.5 years. Over time, employed patients experiencing difficulties with job performance fell from 56% to 6%.¹³⁹

The studies undertaken in Botswana, India and South Africa each show some degree of benefit from the provision of effective treatment to HIV/AIDS patients, indicating that the benefits in terms of economic activity apply across markets.¹⁴⁰

Socio-economic benefits can also be derived from the perception that patients have of their quality of life. As simpler and more efficacious treatment regimens are becoming more and more available, perceived clinical improvements are no longer limited to improvements in mortality and DALYs, but also pertain to the patient's quality of life. Deterioration in quality of life can be directly related with symptoms of depression and anxiety, which in turn can not only further compromise the immune system but also affect behaviour patterns and negatively influence adherence to treatment due to perceived difficulty of the regimen.¹⁴¹

A literature review of various developing countries (including BRICS) studied the effect of ART on quality of life of patients in these countries. The study reported that patients on ART exhibit significant improvement in terms of their quality of life.¹⁴²

- Brazil – A study on overall quality of life of patients enrolled into the ART programme in Brazil found that after 4 months, 66.4% classified their quality of life as either good or very good. The authors made a comparison to another study on HIV/AIDS patients in Bangalore, India, where the self-perception on quality of life was significantly lower (18% said they had a good quality of life). The authors state that this variance is likely due to the fact that there was free and universal coverage for HIV/AIDS in Brazil at that time, making conditions more favourable for patients in Brazil than in India.¹⁴³
- South Africa – In the Free State Province, a study assessing the physical and emotional quality of life was undertaken on a population of patients enrolled in the ART programme. The results of the study showed that patients reported overall

138 Muirhead et al. (2006), 'Health care costs, savings and productivity benefits resulting from a large employer sponsored ART program in South Africa', XVI International AIDS Conference.

139 Rosen S, et al (2014). "Effect of antiretroviral therapy on patients' economic well-being: five-year follow-up. *AIDS* vol 28 no.3 pp. 417-424. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3893293/>. [Accessed 13.11.2015].

140 According to World Bank data, South Africa and Botswana are classified as UMICs and India is listed as a LMIC.

141 Campos et al (2009), 'Quality of Life Among HIV-Infected Patients in Brazil after Initiation of Treatment', *Clinics*, 64, 9.

142 Beard et al. (2008), 'Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review', Boston University Centre for International Health and Development, Discussion paper, 11.

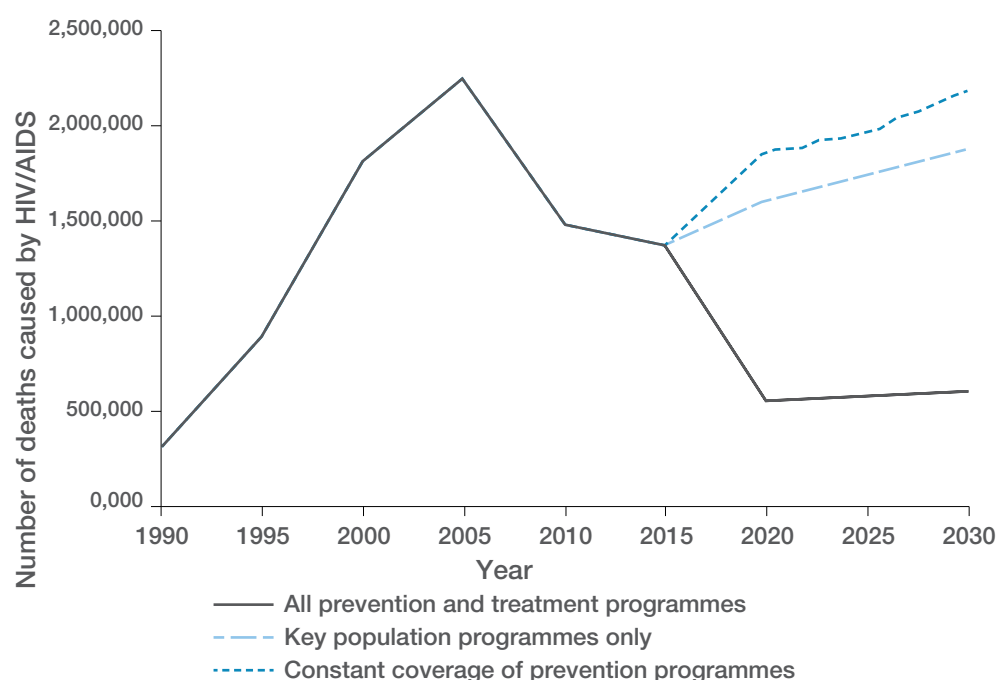
143 Campos et al (2009), 'Quality of Life Among HIV-Infected Patients in Brazil after Initiation of Treatment', *Clinics*, 64, 9.

favourable outcomes in terms of physical and emotional quality of life.¹⁴⁴ Again in South Africa, studies on patients with HIV/AIDS on treatment showed that 86.1% of the patients reported improvements in self-perceived quality of life. It seemed that even qualifying for treatment was perceived as favourable, with 55.3% awaiting ART reporting an improvement in quality of life.¹⁴⁵

2.4. SUMMARY

HIV/AIDS is a severe disease and represented a health policy crisis for many LICs and MICs at the beginning of the century. Significant steps have been made to address this challenge over the last two decades. The number of people living with the disease is stabilising, and the mortality and DALYs level has decreased significantly both in LICs and MICs in general and in the selected countries in this study. Furthermore, the level of transmission between mother and unborn child has decreased significantly. To date around the globe, UNAIDS estimates that almost 36.2 million AIDS related deaths have been avoided between 1990 and 2013. If HIV/AIDS ART coverage continues to expand along with other prevention and treatment services, it is estimated that the number of AIDS-related deaths will further significantly reduce. This scenario is illustrated in Figure 16.¹⁴⁶

Figure 16: Reduction in number of AIDS-related deaths across the globe 1990-2030 under different scenarios



Source: The GAP report, UNAIDS 2014

144 Wouters et al. (2009), 'Physical and emotional health outcomes after 12 months of public-sector antiretroviral treatment in the Free State Province of South Africa: a longitudinal study using structural equation modelling', *BioMed Central*, 9, 103.

145 Beard et al. (2008), 'Non-clinical outcomes of antiretroviral therapy for HIV/AIDS in developing countries: a systematic literature review', Boston University Center for International Health and Development, Discussion paper, 11.

146 UNAIDS (2014), "The GAP report." Available at: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf. [Accessed on 19.11.2015].

It is evident that access to ART, in combination with improvement in prevention and diagnosis, has played a significant role responding to the challenge LICs and MICs faced by HIV/AIDS epidemic.

In addition to clinical and therapeutic benefits, there is also evidence that the introduction of these policies and access to ART is beneficial economically, through reduction in other healthcare costs (such as hospitalisations), and socio-economically, through reduction of absenteeism and improvements in HIV/AIDS patient quality of life. Table 2 provides a summary of the findings within the selected countries.

Table 2: Summary of the findings related to treatment, usage and value of medicines for HIV/AIDS within selected LICs and MICs

	BOTSWANA	BRAZIL	CHINA	INDIA	RWANDA	SOUTH AFRICA
National strategy against HIV/AIDS	2001	1986	2003	During 1980s	2002	2004
Inclusion in EDL	Yes except integrase, and fusion and entry inhibitors	Yes except fusion and entry inhibitors	Yes through Free ART	Yes except integrase, and fusion and entry inhibitors	Yes except integrase, and fusion and entry inhibitors	Yes except integrase, and fusion and entry inhibitors
Patient ART coverage in 2013	70%	46%	59%	36%	66%	42%
Existing evidence on the value of treatment	Clinical, Socio-economic	Clinical, Cost control; Quality of life	Clinical	Clinical; Socio-economic	Clinical	Clinical, Cost control; Socio-economic; Quality of life

Source: CRA analysis

3

POLICY IMPLICATIONS

In the previous section, we have set out the evidence regarding the value of innovative HIV/AIDS treatments deliver to LICs and MICs showing that innovative treatments have benefited patients, the healthcare system and the society.

In this chapter, we draw on the evidence from the case studies to outline policy implications.

THE ESTABLISHMENT AND MAINTENANCE OF HIV/AIDS AS A POLICY PRIORITY

Governments around the globe have implemented national strategies aimed at controlling the HIV/AIDS epidemic by preventing transmission and providing access to treatment. Across countries in this report, improvements in ART coverage were initiated by the national plans –prior to 2000 in Brazil, Botswana and Rwanda and soon after in the early 2000s in China, India, and South Africa. The national plans identified HIV/AIDS as a priority for the government and are associated with increased resources assigned to ensure access to treatment, although the source of funds differs with some receiving financial help from transnational organisations like the World Bank and the Bill and Melinda Gates Foundation (Rwanda), while in others domestic spending has played a greater role (China, Botswana, and South Africa). Considering the estimate that an additional 28 million people could be living with HIV by 2030 if current coverage rates are not improved, it remains vital that these countries, and in particular MICs like India and China, maintain HIV as a national priority.¹⁴⁷ Indeed, the need to keep HIV/AIDS at the forefront of national policies has been advocated by the WHO and UNAIDS.^{148,149,150}

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. This remains vital today

INVESTMENT IN HEALTHCARE INFRASTRUCTURE

The increased provision of ART to patients with HIV/AIDS is associated with investment in healthcare infrastructure. Without patients being identified, diagnosed, tested and appropriately managed, it is not possible to increase access and, unsurprisingly, we are then unlikely to observe benefits from medicines in LICs and MICs. Unsurprisingly, countries that devote more spending on health and HIV related services are associated with greater ART coverage, which in turn, contributes to the accumulation of

147 The Times of India (2016). “Budget cuts for NACO hits HIV/AIDS control programme” Available at: <http://timesofindia.indiatimes.com/city/visakhapatnam/Budget-cut-for-NACO-hits-HIV/AIDS-control-programme/article-show/52286050.cms>

148 WHO (2014) “HIV, universal health coverage and the post-2015 development agenda – A discussion paper”. Available at: <http://www.who.int/hiv/pub/toolkits/universal-coverage2014/en/>. [Accessed 08.02.2016].

149 UNAIDS (2015). “How AIDS changed everything – MDG6 15 years, 15 lessons of hope from the AIDS response.” Available at: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf. [Accessed on 08.02.2016].

150 UNAIDS (2016). “Fast-track Ending the AIDS Epidemic by 2030.” Available at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.

value from ART. For example, Botswana's early introduction of universal health coverage for ART significantly increased access to HIV treatment and reaped a reduction in the prevalence of HIV.¹⁵¹

All selected LICs and MICs in this report have recognised the need for infrastructure, and have followed through by including investment in infrastructure in their national plans. Again, in Botswana, where ART is provided across the population, most of the allocated government resources are designated to support AIDS prevention, care and treatment. The plan was successfully implemented and has brought benefits from different perspectives. Botswana not only has received the most therapeutic/clinical value from ART among study countries, but also has experienced reduction of absenteeism linked to HIV/AIDS since implementing the program. In India, national initiatives include an objective of "building capacity at national level". As a result, the government estimates that on an annual basis, between 50,000 to 60,000 AIDS related deaths can be averted.¹⁵²

Healthcare centres built to diagnose and distribute ART and the infrastructure to facilitate patient access to those centres also helps address other infectious and non-communicable diseases. With the UNAIDS goals to increase access to 90% of all HIV patients by 2020 and 95% by 2030, the need for continued and increased spending on HIV/AIDS to build capacity in HIV management and services is clear (as recommended in recent reports by international organisations).^{153,154,155}

For medicines to deliver value, there needs to be appropriate healthcare infrastructure, this works best when integrated programmes are used to ensure diagnosis, testing, access to medicines and maintenance of patients on a course of treatment

THE GENERIC INDUSTRY AND THE INNOVATOR INDUSTRY CONTRIBUTE IN DIFFERENT WAYS TO ADDRESSING THE EPIDEMIC

Innovators have been responsible for all of the significant new medicines treating HIV over the last decade. However, both the generic industry and the innovative industry have and continue to contribute in different ways to addressing the epidemic. In some situations, generic companies are able to supply low-income countries more efficiently and more cheaply than innovating companies. Innovating companies should also 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.

151 WHO (2014), "Country Cooperation Strategy – Botswana." Available at: http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_bwa_en.pdf. [Accessed on 08.03.2016].

152 Department of AIDS Control, Ministry of Health & Family Welfare, Government of India "National AIDS Control Programme Phase-IV (2012-2017)." Available at: <http://www.naco.gov.in/upload/NACP%20-%20IV/NACP-IV%20Strategy%20Document%20.pdf>. [Accessed on 16.11.2015].

153 UNAIDS (2016), "Fast-track Ending the AIDS Epidemic by 2030." Available at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf.

154 WHO (2014) "HIV, universal health coverage and the post-2015 development agenda – A discussion paper". Available at: <http://www.who.int/hiv/pub/toolkits/universal-coverage2014/en/>. [Accessed 08.02.2016].

155 UNAIDS (2015). "How AIDS changed everything – MDG6 15 years, 15 lessons of hope from the AIDS response." Available at: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf. [Accessed on 08.02.2016].

To this end, we have seen that voluntary licensing and differential pricing are increasingly common. Despite the concern that intellectual property rights can impede access to HIV treatment, we find very few examples of compulsory licensing in LICs and MICs over the last decade. Moreover, in our statistical analysis, we do not find there to be any relationship with the extent of ART coverage. Instead, we find there is an increasing trend in the use of voluntary licensing and that both patented and off-patent products have a role to play in delivering value to LICs and MICs. Looking ahead, we expect the generic and innovative industry to continue with their roles in improving access to HIV medicines. There is an obvious need for the innovative industry to continue investing in the development of new therapies for HIV.

The healthcare system should encompass in-patent and off-patent medicines

A WIDE DEFINITION OF VALUE SHOULD BE RECOGNISED

ART have delivered a broad range of benefits affecting not only patients but also the healthcare system and the society in general. We found evidence of value being delivered through reduced healthcare costs and through benefits to the wider economy. In South Africa, we observed clinical benefits, healthcare cost savings and large societal benefits in terms of reduced absenteeism. Similar to South Africa, we observed productivity gains in India and Botswana due to ART. In terms of allocating resources to HIV/AIDS, a holistic approach taking into account the full range of benefits is important.

In LICs and MICs, the value medicines needs to be considered holistically as they deliver value directly to patients, to the healthcare system, and to the wider society.

**APPENDIX: A STATISTICAL
ANALYSIS OF THE FACTORS
DETERMINING ACCESS**

In order to identify the relative importance of each factor on determining access to ART across countries and over time, we have undertaken a statistical analysis.

METHODOLOGY FOR STATISTICAL ANALYSIS

The objective of the analysis is to test whether there is a correlation between measures of access and variables that act as proxies for the different interventions discussed in Chapter 2.2. We undertook a statistical analysis similar to the one in the IFPMA 2011 publication on access to essential medicines.¹⁵⁶

To identify what factors other than income are associated with higher levels of access to ART, we have used the following specification of a linear regression model:

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

Where

- *ARTcoverage* is the percentage of all people with HIV with ART coverage *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 programs were first launched in the country, the total expenditure in HIV programs as a share of the national income and whether compulsory licensing has ever been used in the country;
- *timecontrols* is a vector of dummies introducing year fixed effects into the regression;

We have combined data from different sources. Data on ART coverage rate and expenditures in HIV programmes were referenced from UNAIDS. The start of ART programmes were taken from the WHO. Other country characteristics such as per capita income, health expenditure and HIV prevalence referenced the World Bank. We describe the variables and data used in Table 3 below.

¹⁵⁶ IFPMA and CRA conducted a statistical analysis in the 2011 publication “Evidence on access to essential medicines for the treatment of HIV/AIDS”. Available at: http://www.ifpma.org/fileadmin/content/Publication/2013/web_Brochure_CRA_IFPMA.pdf. [Accessed on 01.02.2016].

Table 3: Description of variables and data sources

VARIABLE	DESCRIPTION	SOURCE
Access measure		
ART coverage rate	Share of HIV-positive adults and children as a percentage of all people living with HIV	UNAIDS
Country characteristics		
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, UNAIDS
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. ¹⁵⁶	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	This takes the value of a 1 after the country has used compulsory licensing	CRA

Source: CRA

These variables set out above are intended to proxy for the policy interventions discussed in Chapter 2.2. 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 national prioritisation of HIV but this is clearly imperfect. The compulsory licence variable captures if this has been not when this has been used. This variable could also capture the effect that the perceived threat of compulsory licensing may have, to the extent that countries that have actually used compulsory licensing are perceived as being more likely to use it again.

¹⁵⁷ It should be noted that the data on the year when ART program started is therefore not necessarily consistent with the data in the last chapter. It would be inappropriate to correct this for the case studies and not for the other countries.

Table 4 describes the data that have been gathered. The dataset contains yearly data at the country level for 93 LICs and MICs with ART coverage data. Although not all countries have observations for the entire period, this dataset provides a comprehensive picture of these dimensions in low and middle income countries over the last five years.

Table 4: Summary statistics for country characteristics and policy interventions

VARIABLE	NUMBER OF OBSERVATIONS	MEAN	STANDARD DEVIATION	MINIMUM VALUE	MAXIMUM VALUE
ART coverage rate (2006 guidelines)	480	27.43	14.99	1.00	71.00
Log of per capita income	467	7.74	1.13	5.37	10.06
Gini index	425	43.83	8.56	29.11	64.79
HIV prevalence rate (%)	270	0.76	2.86	0.00	17.82
Sub-Saharan Africa	480	0.42	0.49	0.00	1.00
Starting year of ART programs	415	2003	2.43	1999	2007
Health expenditure as % of GDP	380	0.06	0.02	0.02	0.12
HIV expenditure as % of GDP	280	0.004	0.007	0.00002	0.04
Foreign HIV aid as % of HIV expenditure	278	0.58	0.33	0.00	1.00

Source: CRA

INTERPRETATION OF THE RESULTS

We have estimated the coefficients in this model by ordinary least squares (OLS) and the resulting estimates are reported in Table 5.

Table 5: Estimates from regressions of ART coverage rates

EXPLAINED VARIABLE: ART COVERAGE RATE	ALL COUNTRIES (1)	ALL COUNTRIES (2)	LOW INCOME	LOWER-MIDDLE INCOME
Log of per capita income	0.561 (0.456)	1.591 (0.177)	1.945 (0.176)	7.951** (0.023)
Gini index	0.608*** (0.000)	0.553*** (0.000)	0.184 (0.101)	0.609*** (0.004)
Sub-Saharan Africa	-0.800 (0.607)	-3.114* (0.082)	-6.080*** (0.004)	-3.182 (0.562)
Starting year of ART programs	-1.900*** (0.000)	-1.728*** (0.000)	-3.444*** (0.000)	0.830 (0.288)
Health expenditure as share of GDP	126.663*** (0.000)		131.868*** (0.002)	5.700 (0.958)
HIV expenditure as share of GDP		654.325*** (0.000)	562.081*** (0.000)	423.270 (0.205)
Foreign HIV aid as share of HIV expenditure		-1.637 (0.648)		

EXPLAINED VARIABLE: ART COVERAGE RATE	ALL COUNTRIES (1)	ALL COUNTRIES (2)	LOW INCOME	LOWER-MIDDLE INCOME
Use of compulsory licensing	-0.853 (0.754)	-2.325 (0.465)	-2.685 (0.423)	-13.329 (0.189)
Dummy year 2011	3.388** (0.05)	3.412* (0.077)		
Dummy year 2012	6.443*** (0.000)	6.585*** (0.001)		
Dummy year 2013	9.712*** (0.000)	8.308*** (0.000)		
Dummy year 2014		13.987*** (0.000)		
Constant	3788.972*** (0.000)	3444.321*** (0.000)	6893.341*** (0.000)	1726.589 (0.274)
Number of observations	295	220	139	56
R squared	0.453	0.509	0.517	0.407

Notes: All countries (1) included all variable except HIV expenditure; All countries (2) included all variables except for total health expenditure. Source: CRA; () represents the significance level. *** is used to denote significance at 1%, ** at 5% and * at 10%

In the first two columns, we present the results for all countries. 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:

- the inequality in the distribution of income within the country;
- the country being outside of the sub-Saharan African region;
- the time since large-scale ART programmes were started;
- the total expenditure on health
- the expenditure on prevention, treatment and management of HIV.

Additionally, we conducted statistical analyses separately for low and lower-middle countries to investigate whether these factors have different importance depending on the group of countries. Estimates are reported in the third and fourth columns of results, respectively:

- income per capita and income distribution are only significant for lower-middle income countries;
- the country being outside sub-Saharan Africa, the time since large-scale ART programmes were started, the total expenditure on health and the total expenditure on prevention, treatment and management of HIV in total are only significant when including low income countries.

These results are consistent with our expectations about the relation between ART coverage and the investigated factors.

It is unsurprising that higher levels of GDP per capita in lower-middle income countries have higher levels of access. When restricting the sample to low-income countries, this correlation becomes insignificant. This is consistent with the fact that HIV programs 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.

We also find that Saharan African countries show lower ART coverage. This might be surprising given the international attention focused on sub-Saharan Africa 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 programs require developing appropriate healthcare infrastructure and capacity, which takes time. It is therefore unsurprising that countries that started their programs earlier are at a more advanced stage in the provision of ART to their patient population. This is especially true for low-income countries that launched the programs earlier, which is sensible if ART programmes are considered a proxy measure reflecting political will to fight the HIV/AIDS epidemic. However, correlation between ART programs and coverage become insignificant for lower and upper-middle income countries.

As a barrier to uptake of antiretroviral drugs for HIV patients in LICs and MICs is the poor service accessibility, a by-product of staff shortages for example, we also expected higher expenditure in healthcare in general and in HIV programs to reduce barriers to ART and we find this in this statistical analysis.^{158,159} As more resources are being invested in fighting HIV locally, then higher shares of patient population are reached and this is especially the case 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.

We do not find the level of ART coverage to be correlated with the use of compulsory licensing.

158 Gourlay et al (2013), "Barriers and facilitating factors to the uptake of antiretroviral drugs for PMTCT of HIV in sub-Saharan Africa: A systematic review". Available at: <http://strive.lshtm.ac.uk/resources/barriers-and-facilitating-factors-uptake-antiretroviral-drugs-pmtct-hiv-sub-saharan-africa>. [Accessed on 08.02.2016].

159 Eholie SP et al (2012) "HIV treatment and care in resource-constrained environments: challenges for the next decade." Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22944479>. [Accessed on 08.02.2016].

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