Expanding Global Access to ARVs in Emerging and Poor Countries in Sub-Saharan Africa: The Challenges of Prices and Patents

Tania M Ngo
Rio de Janeiro - 2017
There was a time when I totally lost hope. Everyone abandoned me: my family, my four brothers, my husband who sent my children away from me, to the village, and threw me out to marry another woman when I started to lose weight. While I was ill, people came to my house and took everything, believing I was going to die. It was so traumatic that I had a relapse. I spent all my money in health centres and hospitals. When all my cash ran out, the centre threw me out. They said “Go home, you’re going to die”. Thankfully a doctor said they couldn’t just let me die like that, so they brought me to MSF’s Kabinda hospital. If I hadn’t come, I would have died.”

37 year old patient, Kinshasa, DRC
Ngo, Tania Mamikana

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EXPANDING GLOBAL ACCESS TO ARVS IN EMERGING AND POOR COUNTRIES: THE CHALLENGES OF PRICES AND PATENTS.

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ASSINATURA DOS MEMBROS DA BANCA EXAMINADORA

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I would like to thank my mother Elise Kana and My sister, Aurelie Ngo. They have supported me with this research from day one and for supporting me morally and spiritually during this program. I would also like to thank my husband Yannick Kayembe who has always encouraged me to keep going even when obstacles present themselves.

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Lastly, I must also thank all of the people I met and work with in Africa, who assisted with my research by sharing their stories, both hardships and successes. It provided me with the motivation to keep writing.
Dedication

To the children in Africa who could brighten even the gloomiest of days with their smiles and positive energy. May you always receive the medication you need in order to win this battle that has been forced upon you.
Abstract

Affordability is a key concern of international donors who finance antiretroviral drugs to treat AIDS in Sub-Saharan African countries. The ability of Sub-Saharan Africa to reduce their prices below large-scale manufacturers in India is challenging. Additionally, these medicines must meet The World Health Organization prequalification standards. While the cost of second-line ARVs remains a concern, donors should also focus resources on other factors of ARV access, such as the supply of human resources for health, infrastructure and issues of sustainable financing.

This research specifically aims to determine if the domestic production of antiretroviral drugs can be a successful and viable option to increase access to ARVs in sub-Saharan Africa by using three case studies of Uganda, Kenya and The democratic Republic of Congo. The research is intended to explore a potentially economical way to provide ARVs to populations with HIV/AIDS in order to move away from a dependence on foreign aid, which does not guarantee continued long-term access to the medications. Since ARVs must be taken daily for the duration of the patient's life, it is important to develop ways to increase access to the medications in a manner that facilitates the long-term drug procurement. The success of local manufacturers then relies on the capacity of the firm to achieve two necessary elements of donor-financed requirements: international quality standards and economies of scale to lower price. I recommend that more countries in Africa should produce ARVs locally in order to lower to cost and increase accessibility, especially in small villages. Even though the current operation of local production has not led to a significant increase in access primarily due to market entry restrictions, this endeavor have the ability to amplify long-term access to affordable ARV drugs.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENT</td>
<td>3</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>6</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>7</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>8</td>
</tr>
<tr>
<td>ACRONYMS AND ABBREVIATIONS</td>
<td>10</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>12</td>
</tr>
<tr>
<td>THE IMPACT OF PATENTS ON ACCESS TO MEDICINES</td>
<td>14</td>
</tr>
<tr>
<td>The access to medicines crisis</td>
<td>14</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>15</td>
</tr>
<tr>
<td>GENERAL</td>
<td>15</td>
</tr>
<tr>
<td>SPECIFIC</td>
<td>15</td>
</tr>
<tr>
<td>LITERATURE REVIEW</td>
<td>16</td>
</tr>
<tr>
<td>METHODOLOGY</td>
<td>19</td>
</tr>
<tr>
<td>ETHICAL CONSIDERATIONS</td>
<td>20</td>
</tr>
<tr>
<td>CASE STUDIES</td>
<td>21</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>21</td>
</tr>
<tr>
<td>THE DEMOCRATIC REPUBLIC OF CONGO</td>
<td>22</td>
</tr>
<tr>
<td>SITUATION ANALYSIS</td>
<td>22</td>
</tr>
<tr>
<td>DOMESTIC ARVs PRODUCTION ATTEMPT</td>
<td>24</td>
</tr>
<tr>
<td>UGANDA</td>
<td>25</td>
</tr>
<tr>
<td>ANTIRETROVIRAL TREATMENT (ART) IN UGANDA</td>
<td>25</td>
</tr>
<tr>
<td>FUNDING OF THE TREATMENT</td>
<td>26</td>
</tr>
<tr>
<td>LOCAL PRODUCTION</td>
<td>27</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>28</td>
</tr>
<tr>
<td>DATA ANALYSIS</td>
<td>28</td>
</tr>
<tr>
<td>KEY FINDINGS</td>
<td>32</td>
</tr>
<tr>
<td>THE PRODUCTION OF GENERIC DRUGS</td>
<td>34</td>
</tr>
<tr>
<td>India’s pharmaceutical industry and its ability to produce ARV drugs</td>
<td>34</td>
</tr>
<tr>
<td>COUNTRIES REPORTING PURCHASE OF INDIAN-PRODUCED GENERIC ARVS</td>
<td>35</td>
</tr>
<tr>
<td>OVERVIEW OF THE MAIN RESULTS</td>
<td>36</td>
</tr>
<tr>
<td>Differential pricing is necessary and feasible</td>
<td>36</td>
</tr>
<tr>
<td>Economic feasibility</td>
<td>36</td>
</tr>
<tr>
<td>Political Feasibility</td>
<td>37</td>
</tr>
<tr>
<td>DISCUSSION OF THE RESULTS</td>
<td>38</td>
</tr>
<tr>
<td>ARV GENERICS</td>
<td>40</td>
</tr>
<tr>
<td>LOCAL PRODUCTION</td>
<td>41</td>
</tr>
<tr>
<td>BENEFITS OF LOCAL PRODUCTION</td>
<td>41</td>
</tr>
<tr>
<td>DIFFICULTIES IN THE PATH TO PRODUCTION</td>
<td>42</td>
</tr>
<tr>
<td>LIMITATIONS</td>
<td>44</td>
</tr>
</tbody>
</table>
Acronyms and Abbreviations

ACP: AIDS Control Program

AIDS: Acute Immune Deficiency Syndrome

APIs: Active pharmaceutical ingredients

ART: Antiretroviral therapy

ARV: Antiretroviral

BRICS: Brazil, Russia, India, China, and South Africa

CSIR: The Indian Council of Scientific and Industrial Research

CSR: Catholic Relief Services

Doha Declaration: The Doha Declaration on the Trade Related Aspects of Intellectual Property Rights Agreement and Public Health

FDA: Federal Drug Authority

FDI: Foreign Direct Investment

Trade Global Fund: The Global Fund for AIDS, Tuberculosis, and Malaria

HAART: Highly Active Antiretroviral Therapy

HIV: Human Immunodeficiency Virus

WHO World Health Organization

WHO/PHI WHO Department of Public Health, Innovation and Intellectual Property

WIPO World Intellectual Property Organization

WTO World Trade Organization
PEPFAR: The US President's Emergency Plan for AIDS Relief

PEA: Private Equity Africa

PhRMA: Pharmaceutical Research and Manufactures of America

QCL: Quality Chemicals Limited (formally known as)

QCIL: Quality Chemical Industries Limited

RoU: Republic of Uganda

SCMS: Supply Chain Management System

STD: Sexually Transmitted Disease

TASO: The AIDS Support Organization

TB: Tuberculosis

TLG: TLG Capital Fund

TPI: Tanzanian Pharmaceutical Industry Limited

TRIPS: Trade Related Aspects of Intellectual Property Rights

UAC: Uganda AIDS Commission

UNAIDS: The Joint United Nations Program on HIV/AIDS

UNGASS: United Nations General Assembly Special Session

UPMA: The Ugandan Pharmaceutical Manufacturers' Association

US: United States

US AID: United States Agency for International Development

USD: United States Dollars
Introduction

Despite the countries proposed achievements in Fighting HIV/AIDS, the prevalence rate of the virus in Africa has continued to result in significant challenges to development. The gravity of the HIV emergency remains enormous.

Twenty years ago, the subject of Human Immunodeficiency Virus (HIV), which has been found to be the cause of Acquired Immunodeficiency Syndrome (AIDS), would not have been the topic of a major and serious worldwide catastrophe. People were not phased by the effects that would be caused by this ever so populating disease, and no one would have ever realized that this disease would not be curable or helped without expensive medicine.

The origin of AIDS remains unknown. In one theory, it is believed that the disease originated in Haiti and was transported to Africa in the mid 1960s when a large number of Haitians immigrated to The Democratic Republic of the Congo, then called Zaire. In another prominent theory, however, it is believed that AIDS originated in Africa by means of a virus similar to HIV found in the African green monkey. According to this theory, the precursor virus may have moved from subhuman primates to people relatively recently, or it may have been present in a few resistant carriers from previously isolated tribes for a long time and was just recently transmitted to the cities by migration. There is evidence to support and dispute both theories, however, and it remains uncertain exactly when or how AIDS began in the world.

There is no question that an epidemic in these proportions would disrupt the economic and social aspects of a nation, but without a doubt, the political economy of the nation would also be disrupted.

According to the 2015 WHO/UNAIDS estimates, more than 95% of HIV infections are in emerging countries, two-thirds of them in sub-Saharan Africa, where over 28 million people are living with HIV. While infection rates are lower in Asia and the Pacific, where over 7 million are infected, there is a risk that localized epidemics involving mainly high-risk groups could spark off major epidemics in some of the world’s most populous countries.
From an economic standpoint, high AIDS rates have contributed to a significant decrease in the productive workforce as many laborers are simply too sick to attend their jobs. As well, many family members are forced to forgo their livelihoods in order to take care of their ill relatives. In particular, AIDS has led to a decline in the agricultural productivity levels of many countries in Sub-Saharan Africa (International Labor Organization [ILO], 2010). The loss in productivity within the agricultural sector has even resulted in the occurrence of AIDS induced famines, and in 2012 14 million were at risk of starvation (UNAIDS, 2013).

Poverty is increasing in many countries as households lose one or more breadwinners to AIDS. And both public services and private companies are reeling from the impact of HIV-related sickness and deaths among their workforce.

Being the founder of a non-profit that works in the Democratic Republic of the Congo, Burkina Faso, and Togo, I have a first hand experience on how the affordability and accessibility of ARVs remains a challenge, especially in the rural areas. Even though some countries in Africa have announced a free HIV treatment for its population, it has not been enough to eliminate the high and sometimes inequitable economic burden of HIV/ AIDS on households. Most of the time, the free treatment can be obtained at only a few designated facilities in the country. Exorbitant food and transport costs, as well as the costs of illnesses linked to HIV, hinder full access to treatment services.

On the other hand, Pharmaceutical markets in low resource settings are imperfect. Suppliers provide in formation on ‘suggested’ medicine prices, but actual purchase prices vary substantially across purchasers and these prices paid are typically unavailable. Most generic ARVs are cheaper than branded counterparts, with the exception of protease inhibitors (PIs) in which some generic versions are more expensive than branded counterparts. Less price variation is noted for ARVs in low-income countries than middle-income countries. In order to meet global goals of universal access to HIV/AIDS treatment, further price reductions are needed for ARVs.
New approaches are needed to create incentives for generic manufacturers of these ARVs to enter the market and create price competition with these medicines. On the other hand, local production has been proven to drastically reduce the price of ARVs.

The impact of patents on access to medicines

The access to medicines crisis

Patents\(^1\) can have a dramatic impact on access to medicines when they are used to prevent competition. A drug company that holds patents on a medicine has the right to prevent others from manufacturing it and therefore can charge an artificially high price. When a company is selling cellphones or pens for example, this might be of no great significance. However, when life-saving treatments for diseases, such as HIV/AIDS become unaffordable to those that need them, the consequences can be - and are - devastating. In developing countries, where people pay for drugs out of their own pockets and very seldom have health insurance, the high price of medicines becomes a question of life and death.

\(^1\) A government authority or license conferring a right or title for a set period, especially the sole right to exclude others from making, using, or selling an invention
Objectives

General

- Analyze initiatives aiming to improve access to medicines through market interventions must take into account the interconnectedness of health policy, industrial organization, economic development and political factors at both global and national levels.

- Examine the need to expand the dialogue about access to medicines beyond the effects of policies on medicine prices.

Specific

- Analyze the role of Indian generic manufacturers in supplying ARV medicines to developing countries in Africa.

- Explain that local production of ARVs will drastically decrease the price of ARVs and expand global access.

- Encourage partnerships among other sub-Saharan countries for those who have not enough resources for a domestic production.
A healthy population tends to act as a primary indicator of a developed nation.

The high prevalence rate of HIV/AIDS in Sub-Saharan Africa acts as an overwhelming challenge to development in the region. The virus not only causes immense physical and emotional suffering but exacerbates issues that threaten livelihoods across the African continent. Lewis (2013) maintains that the impact of the disease has created a pressing moral demand to find solutions to improve access to treatment and care. According to him, the virus puts an enormous burden on the economies of the countries faced with the highest rates.

Agbonifo describes a healthy nation as one where, "the mental and physical needs of the generality of its citizens are adequately met" (Agbonifo, 1983, p. 2003). These needs refer to strong levels of nutrition; proper hygiene, not only on an individual basis but in reference also to the environment one lives in; sufficient infrastructure including water facilities and shelter; and adequate health care services (1983). Thus, the good health of a nation can be reflective of its development achievements.

Academics have noted that many countries with already weakened economies, and equally frail resources, face the struggle of attempting to support the large population of HIV positive patients through costly treatment and drug therapies (Sachs, 2015). The weight of the epidemic has further drained the preexisting minimal government resources available to deal with the breath of such costly emergencies.

Besides affordability other factors play a crucial role in determining access to medicines, especially availability of adequate, sustainable and equitable financing. International aid programs, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States President’s Emergency Plan for AIDS Relief (PEPFAR), UNITAID and Advance Market Commitments for vaccines (AMC) respond to the rationale of channeling resources for the purchase of drugs and vaccines.
While some diseases are stronger catalyst for such programs, further support is needed for other chronic, non-communicable diseases. In 2012, Roger England (chairman of Health Systems Workshop a health-policy charity) raised the controversial question “Are we spending too much on HIV?” on the authoritative British Medical Journal.

Dr. England pointed out that AIDS receives about a quarter of global health aid but accounts for “only 5% of the disease burden in low- and middle-income countries”; in his view efficiency improvements in health systems would be more effective if aimed at broader goals like tackling other diseases and by means of less inexpensive interventions such as immunizations. Further evidence on cross-country disparities from a study by the Economic and Social Commission for Asia and the Pacific (UNESCAP) \(^1\) shows that per capita spending on pharmaceuticals ranges from less than $20 in low- and middle-income countries to $528 in high-income countries. The key point is that differences are also significant in the distribution of research and production capacity.

One of the suggested pathways towards the removal of barriers to essential drugs is the development, or strengthening, of local production systems. In some low-resource settings activities are limited to compounding and packaging, repacking, and processing bulk medicines into dosage forms using imported raw materials; in the few countries where production takes place, it is mostly for generic medicines and aimed at a small proportion of domestic demand. It is clear that the viability of such local production system depends on a variety of economic, social and institutional factors. The key activities involved in the production of pharmaceutical drugs include:

- Manufacture of products by chemical synthesis;
- Production and separation of medicinal chemicals

However, a World Bank report by Lashman argues against the local manufacturing argument on the grounds that the prevailing conditions within LDCs do not meet minimum operational and

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\(^1\) Established in 1947 with its headquarters in Bangkok, Thailand, ESCAP works to overcome some of the region’s greatest challenges by providing results oriented projects, technical assistance and capacity building to member States in diverse areas.
technical standards that are necessary to set up local production of medicines. Notable exceptions were countries with large local markets and potential to produce Active Pharmaceutical Ingredients (APIs) such as China, India, Thailand, Brazil, and Argentina.

Kaplan et al, Chauduri, and Loureiro et al concur that recent changes in the global economy place countries like China, Brazil, Korea and India in a better position to compete on a global scale and in pharmaceutical production also. A different picture emerges for Sub-Saharan African countries where structural deficiencies are still persistent and a significant obstacle to escape the poverty trap. Besides structural deficiencies in financial and human resources local pharmaceutical markets suffer from lack of regulation and government supervision, which reduce the prospects of industrial expansion (Chauduri, 2013).

A study by the World Health Organization reiterates that growing pressure from foreign competition forced scaling down activities of local pharmaceutical industries in 38 countries of Sub-Saharan Africa (WHO, 2005). The broader point is that poverty tends to be a self-reinforcing process aggravated by circumstances such as shortage of skilled labor, scarcely developed financial sectors, low levels of foreign direct investment, inefficient systems for financing, taxes and regulation, corruption and generally weak legal and regulatory regimes. The challenge of competing within a global pharmaceutical market adds other factors to that list: restrictions from intellectual property right regimes, wide fluctuations in cost per unit, ineffective measures against unfair practices like dumping, add to these factors (see Kaplan et al; Chauduri).

The strong message coming from the specialized literature is that government action is deemed both indispensable and, at the same time, crucial for avoiding the self-reinforcing spiral of low development. This point is advanced forcefully by a study Mackintosh and Tibandebage on the adverse effects of market dynamics in Tanzania where the diffusion of unregulated competition lowers incentives to provision of skilled patient care; where local small businesses are thwarted by systematic instability; and where fragmentation is a leading cause of insufficient and unequal access to health-care for large parts of the population. These concerns are at root of a wider debate
as on how to integrate policies aimed at stimulating innovation with those aimed at ensuring the widest spread of the associated social benefits

Methodology

I have utilized transactional data containing 17,646 donor-funded purchases of ARV tablets made by 115 low- and middle-income countries from 2010 to 2016 to measure market share, purchase trends and prices of Indian-produced generic ARVs compared with those of non-Indian generic and brand ARVs.

I have also conducted search electronically using the following key terms: HIV, AIDS, ARV, ART, HIV Generics, WHO, Sub-Saharan Africa, Low-mid Income Countries. Reviewed articles and publications from 2010 to date, written in English and French were retrieved using search engines like Google Scholar, MEDLINE, PubMed etc. All articles published from 2008 and below and those written in other languages apart from English and French were excluded.

I have conducted studies to understand the rapid emergence of a vibrant and competitive market for antiretroviral medicine following the establishment of global funding initiatives for treatment of HIV/AIDS. I have also examined the impact of large-scale global policies on prices of antiretroviral medicines and in so doing refutes conventional wisdom around mechanisms to lower medicine prices.

Additionally, some of the methods used in this study include case summary, review, systematic cleaning and validation of data, synthetic review of the literature, systematic review of the literature, qualitative descriptive cross sectional design, and cross sectional qualitative survey design with in-depth interview.

I personally travelled to Kinshasa, DRC to conduct in-depth interviews, observations, and to received review of different case summary by the PNMLS and WHO. Despite the request of money and other arrangements in order for me to get access to some data, I was able to work some key people that were of tremendous help.
Participants were expected to either answer a series of questions via email or over the phone. The interviews took any time between 10 and 30 minutes to complete depending on the information that participants were providing. The nature and type of the interviews are not expected to cause any physical harm to participants, and there are no anticipated risks that taking part in this study will be detrimental to the interviewees. Participation in this study was completely optional and voluntary.

**Ethical Considerations**

*Informed consent*

The informed consent process involved the data collector giving a verbal explanation to each potential participant on the nature of the study, its purpose, the procedures involved. Each potential participant was also informed that participation in the study was completely voluntary and that they could withdraw at any time.

The participants were also assured that all information gathered would be treated as confidential and would be accessible only to the researchers, who would be responsible for its safekeeping. There would be anonymity in the reported findings, unless we obtained approval for a picture or a quote.
Case Studies

Introduction

This study was part of a three-country study on access and pricing of ART, which included The Democratic Republic of Congo, South Africa and Uganda. Fieldwork took place in in East Africa, Central Africa, and Southern Africa, specifically in Kampala- Uganda; Kinshasa – DR Congo; Pretoria – South Africa.

Technical advice was provided by the PNMLS and by the WHO

Summary of Indian-produced generic ARVs for countries with highest purchase volumes

<table>
<thead>
<tr>
<th>Purchase volume rank</th>
<th>Country</th>
<th>% of ARV volume supplied by Indian generic producers</th>
<th>Value of Indian-produced generic ARV purchases (USD million)</th>
<th># Indian-produced generic ARV dosage forms purchased</th>
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<tr>
<td>1</td>
<td>India</td>
<td>100</td>
<td>25.9</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>United Republic of Tanzania</td>
<td>96</td>
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<td>13</td>
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<tr>
<td>3</td>
<td>Nigeria</td>
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<td>4</td>
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<td>96</td>
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<td>10</td>
<td>Cameroon</td>
<td>93</td>
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Source: ncbi.nih.gov
The Democratic Republic of Congo

Situation Analysis

The Democratic Republic of the Congo was among the first African countries to design and implement a program for HIV/AIDS awareness and prevention in the early 1980s. In 1987, the government established the National AIDS Control Program to lead the fight against a rapidly increasing epidemic. However, progress was interrupted by the political and civil crisis that broke out in the mid-1990s.

A National Strategic Plan for an integrated response to HIV/AIDS was adopted, including prevention, care and interventions related to the provision of antiretroviral therapy and essential drugs to treat opportunistic infections. A National Health Sector Plan for HIV/AIDS was also developed.

In January 2005, the Democratic Republic of the Congo finalized its National Strategic Plan for Scaling Up Access to Antiretroviral Therapy. The Plan includes strategies for training additional health workers to deliver antiretroviral therapy, expanding prevention and care facilities, strengthening the capacity of national laboratories and improving the procurement and supply management systems for antiretroviral drugs and other supplies. A total of 74 health workers had been trained to deliver antiretroviral therapy in accordance with national standards, mostly in Kinshasa, the capital.

However, many years of civil unrest have damaged the health care delivery system. The country is large, has a sizeable mobile population and health care services are inadequately decentralized. There is a severe shortage of human resources trained to deliver antiretroviral therapy. Access to antiretroviral therapy is limited in many provinces. Systems for procurement and supply management of drugs are inadequate, and the cost of treatment remains high. Coordinating mechanisms and monitoring and evaluation systems need to be strengthened. Rapidly scaling up HIV prevention, treatment and care requires accelerating the training of health workers, expanding services for voluntary counseling and testing and preventing mother-to-child transmission,
reducing the cost of antiretroviral drugs and diagnostics, extending coverage of services to rural areas and reinforcing synergy among the activities of various partner organizations.

Resource requirements and funds committed for scaling up treatment and prevention

- WHO estimates that between US$ 84.6 million and US$ 88.3 million was required to scale up treatment in the Democratic Republic of the Congo and reach the WHO “3 by 5” treatment target of 80,000 people.
- The Democratic Republic of the Congo submitted a successful funding proposal to the Global Fund to Fight AIDS, Tuberculosis and Malaria in Round 3 with a total funding request of US$ 113.6 million and approved two-year funding of US$ 34.7 million. The proposal covers a range of HIV prevention and care activities, including providing antiretroviral therapy. It also focuses on monitoring and evaluating the program and training health personnel.
- The World Bank Multi-Country HIV/AIDS Program for Africa allocated US$ 102 million in support of the implementation of the country’s national multisectoral strategic plan for HIV/AIDS. Of these funds, US$ 1.2 million was expected to be available for purchasing antiretroviral drugs.
- The Democratic Republic of the Congo is a beneficiary of the sub-regional Great Lakes Initiative against AIDS supported by UNAIDS and the World Bank, which provides support for refugees from outside the Democratic Republic of the Congo, internally displaced populations and refugees from the Democratic Republic of the Congo returning to their homeland. Some support is also available from the Oubangui-Chari initiative of the African Development Bank and UNAIDS, which focuses on prevention activities in the Central African Republic, Congo and the Democratic Republic of the Congo.
Domestic ARVs Production Attempt

Pharmakina\(^1\) has produced generic ARVs since April 2005 in the eastern province of Bukavu, the first pharmaceutical firm to do so in central Africa, but it is now forced to await approval from the World Health Organization (WHO). Pharmakina's generic version of a three-in-one drug combination of Stavudine, Lamivudine and Nevirapine, is called 'Afri-Vir'. The Congolese authorities gave the medication the go-ahead in June 2005, allowing Pharmakina to supply the local market.

Dr Andre Adanji, WHO's humanitarian action in crisis focal officer in Bukavu, confirmed the international agency was running tests on Pharmakina's product. "We've already received samples and these have been sent to Geneva for testing," he said, adding that in principle, WHO supported the production of ARVs by Pharmakina, but needed assurances on quality before allowing the product to be used and/or exported out of the DRC.

"We can produce to a capacity of 180,000 pills a month. Unfortunately, apart from a few private individuals there is no real demand at present," said Dr Pierre Mulema, head of Pharmakina's HIV/AIDS department. "We have the capacity to produce ARVs to meet the demands of all in the DRC and still export to neighboring countries," insisted Mulema. "There is a real need in the DRC for good quality ARVs."

Pharmakina is urging the government and leading NGOs to get behind the concept of local production and resolve the difficulties of acquiring ARVs. MSF Holland, which currently imports ARVs from Amsterdam, says it was considering procuring drugs from Pharmakina.

"By producing locally we stand the chance of saving thousands of lives simply by saving time and cutting costs," said Mulema. "What really hurts is that we have the ARVs available, that are of a good quality, and there are patients who need ARVs who can't access them."

\(^1\) Pharmakina SA is an agro-industrial and pharmaceutical enterprise located in Bukavu, in the South Kivu of the DR Congo (on the shore of the lake Kivu)
Antiretroviral treatment (ART) in Uganda

A survey in 2013 reported 1,478 health facilities in operation in Uganda offering antiretroviral treatment (ART) and that by 30 September 2013, nearly 800,000 people living with HIV were enrolled on treatment. According to the 2010 World Health Organization (WHO) guidelines for ART, the proportion of all ART-eligible people living with HIV that were on treatment by the end of September 2013 in Uganda was 69.4%. However, the introduction of the 2013 WHO treatment guidelines mean that ART access now only stands at 40% for adults and 22% for children.

Funding of the Treatment

Uganda’s experience has shown that donor funding is unpredictable; therefore, not a guarantee.

PEPFAR (US Presidential Emergency Fund for AIDS Relief) is the major contributor to the international funding of HIV and AIDS around the world, particularly to African countries including Uganda. However, there are indications that PEPFAR is facing a number of global issues, such as competing health and development demands across Africa; an ever-increasing burden of HIV/AIDS treatment; and continuous resource constraints due to global financial crisis and increasing domestic deficit.

With this being the case, more efforts have to be made by Uganda to increase their domestic resource mobilization. The concentration of donor funding for HIV among a very small number of donors in Uganda suggests potential vulnerability should the magnitude of their funding commitments change in the future.
The current distribution of free ARVs through the AIDS Control Plan (ACP) is somehow rooted in the Ugandan Government's recognition of the disease and its strategy to address the problem of HIV/AIDS.

At the time President Museveni just came to power, AIDS was still a highly stigmatized disease across the world and particularly in Sub-Saharan Africa. His open and active approach to dealing with the epidemic was regarded by many as groundbreaking for the time (Kinsman, 2010). The implementation of the ACP would later set the stage for the introduction of ARV medication to treat the large population that was suffering from AIDS.

Kinsman (2010) proposes that instead Museveni’s interest in the disease was politically motivated and reflected his desire to maintain healthy military troops to assure his own electoral stability. She also suggests that Fidel Castro played a significant role in drawing to Museveni's attention the problem of HIV/AIDS (2010). She explains that Castro, who had previously recognized the impact of the disease in Cuba, had supported Museveni's army and realized that the disease was evidently present amongst the Ugandan troops.

**Local Production**

In 2007, a partnership was formed between the Government of Uganda, the Ugandan pharmaceutical company, Quality Chemical Industries Limited (QCIL), and the Indian generic drug-manufacturing corporation, Cipla. The drug factory in Luzira, a suburb outside of the capital Kampala, began to produce generic ARVs in 2007, with support from Cipla.

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1 Yoweri Kaguta Museveni is a Ugandan politician who has been President of Uganda since 29 January 1986

2 According to a 2007 published report, it was the only company in Africa that manufactured triple-combination antiretroviral (ARV) drugs
All ARVs purchased with government funding for supply in public clinics and institutions are procured directly from QCIL. However, presently all multilateral and non-governmental organizations in Uganda are not purchasing ARVs from the factory. Particularly, the organizations receiving funding from the United States (US) Government are restricted from procuring any medicine produced at the factory based on the organization's official policy. Since many government clinics and hospital wings partner with and receive funding from American organizations, they are unable to buy drugs produced within Uganda. This factor acts as a substantial barrier to entry into the market for ARVs for QCIL, and impacts its cost recovery phase as well as its ability to achieve economies of scale by increasing the productive capacity of the plant.

South Africa

Data Analysis

The government of South Africa is now self-funding for programs that reach 72% of people receiving HIV/AIDS treatment in a country that is thought to represent approximately 25% of the global (low and middle income) market for ARVs. Decisions made by “market anchor” countries like South Africa have ripple effects beyond their borders. Countries in the surrounding regions are increasingly looking to harmonize their policies, guidelines, and standards to those of dominant countries rather than global players.

South Africa's HIV budget will have to increase by 50% to 60% in the next five years to total about R35-billion a year by 2020 if the country is to provide treatment for everyone with HIV and reach United Nations targets.
This is the finding of one scenario¹ in the health department's HIV and tuberculosis (TB) investment case published in March 2016. The country will implement World Health Organization guidelines, which recommend that all people with HIV should be on lifelong treatment regardless of their CD4 count², which is used to measure the immune's system's strength. Currently, most HIV-positive people in South Africa must wait until their CD4 counts fall to 500 to access Antiretrovirals (ARVs).

By the end of March, 3.4-million people were on treatment, but South Africa has 6.8-million people with HIV, according to health department data. The number of people on ARVs would have to double to meet the new guidelines.

Treasury data show that the country's conditional grant for HIV has grown from R1-billion since its introduction in 2003/2004 to R15.3-million in 2016. This is likely to reach R20-billion by 2018/2019.

¹ http://bhekisisa.org/
² CD4 count is a lab test that measures the number of CD4 T lymphocytes (CD4 cells) in a sample of your blood. In people with HIV, it is the most important laboratory indicator of how well your immune system is working and the strongest predictor of HIV progression.
The total costs of South Africa's HIV program are expected to outstrip projected domestic funding in the next three years, leading to funding gaps. (Source: South Africa's HIV and TB investment case)

South Africa is one of the few developing countries that carry the bulk of the cost of its HIV program. The treasury's chief director for health and social development, Mark Blecher, said the government has "consciously chosen to fund over 80% to 85% of the epidemic, or multiple epidemics, with domestic public funds because it's our duty and responsibility as government to do so".

"General taxation continues to be the most important source of financing," he said. "Despite the fact that South Africa is currently experiencing a period of significant fiscal constraints government will continue to prioritize HIV and TB."
The investment case projects that the portion of HIV funds covered by the government will continue to rise, but there is likely to be a substantial "resource gap" for each year in the next five years.

Health Minister Aaron Motsoaledi said one of the ways to pay for the increased demand in treatment is for the government to negotiate cheaper prices for the medicine.

"If we calculated the amount of money that was going to be needed, based on 2002 estimates, to put 3.4-million people on treatment, it would have added up to around R40-billion," he said.¹

"But that did not happen because we were able to negotiate a more than 50% drop in the price of ARVs per patients to R314 per month. Soon after that we introduced the fixed-dose combination [ARV] and the cost went down to R89, meaning that we could double the number of patients without getting more money from treasury."

South Africa has two main donors, the Global Fund to Fight Aids, TB and Malaria and the United States President’s Emergency Plan for Aids Relief (Pepfar), which assist it to fill financial gaps in its HIV program.

The US government's global Aids coordinator, Deborah Birx, said: "We should be making sure that the dollars have maximum impact by coordinating with the government and the Global Fund and any other bilateral donor. "This is not the time to withdraw funding; this is the time to support South Africa to end its epidemic."

¹ South Africa Budgeting for health - Section 27

² The President’s Emergency Plan For AIDS Relief (PEPFAR/Emergency Plan) is a United States governmental initiative to address the global HIV/AIDS epidemic and help save the lives of those suffering from the disease, primarily in Africa. Pepfar has focused its donor funding in South Africa on population groups and areas with the highest HIV infection rates.
Key Findings

Generic competition as a catalyst for price reductions

The most effective and sustainable way to bring down the price of a drug is through competition between different manufacturers. But if a medicine is under patent and the patent owner is not willing to allow competition, the impact on a drug’s price is striking.

The drugs to treat HIV/AIDS provide a perfect illustration of how patents allow manufacturers to keep the price of medicines high, and how competition brings those prices down. When MSF began providing antiretroviral treatment to people living with HIV/AIDS in 2000, a year’s treatment course cost more than US$ 10,000 per person. At this time, Antiretrovirals (ARVs) were only available from the drug companies that held the patents. With the onset of competition among multiple producers, prices began to plummet in the years that followed. The most commonly used triple-drug AIDS treatment in the developing world now costs less than $70 per year.

This 99% price reduction was possible because the medicines were not under patent in several countries with pharmaceutical production capacity – such as Brazil, India and Thailand – allowing local producers in these countries to legally manufacture generic versions of the medicines patented in developed countries, thereby driving prices down. These affordable generics could also be exported to other developing countries where the medicine was not under patent.

Why the price crisis is set to return

Generic competition may have been instrumental in bringing down the price of the first generation of ARVs and other drugs, but the situation today is different and the progress achieved is once again under threat.

Key countries where generics are produced now grant medicine patents, in order to comply with their international obligations as members of the World Trade Organization. Newer drugs are already patented in these countries, including (but by no means limited to) new ARVs, meaning that production of affordable generic medicines is now restricted.

If generic competition is unable to come to the rescue, newer life-saving medicines will quite simply be priced out of reach of those in need. For HIV/AIDS, this means that countries with
successful AIDS treatment program like Brazil or Thailand face a financial time bomb: patients on treatment gradually need to shift to newer, more expensive drugs as, inevitably, their resistance to older therapies increases, they develop harmful side effects, or as better drugs are developed.

At the same time, the global pattern of diseases is changing. Chronic or non-communicable diseases, such as cancer, diabetes or cardiovascular disease are rapidly increasing in the developing world – and a strategy to get affordable medicines to treat these conditions needs to be put in place now.

But for all newer medicines, now that more and more countries apply tighter patent regimes, competition with affordable generics will be much more limited.

While there is no doubt that generic competition stimulates the reduction of drug prices and increases affordability, the debate over domestic manufacturing in developing countries remains polarized. Advocates argue domestic production increases access to essential medicines; strengthens long-term health security, self-sufficiency and employment while also saving foreign exchange. However, research contends that a local manufacturing industry is often not a viable alternative for developing countries and does not necessarily reduce prices compared to imported drugs. The South African National Economic Development and Labor Council found that 80% of a manufacturer’s profits on a generic drug would be captured within eighteen months of the originator drug coming off patent. Therefore, unless a generic manufacturer is one of the first to enter, the ARV market essentially becomes commodity-based and price is the distinguishing factor among products.
**Infrastructure requirements for factories that produce ARVS**

- Availability of pure water, stable electricity, and gas supplies, and an adequate system for medicine transport.
- Development of human resources consisting of skilled professionals and technician with expertise in pharmaceutical development, quality control, quality assurance, manufacturing processes, regulatory affairs and engineering for pharmaceutical industries.
- Establishment of a diversified portfolio including other medicines to guarantee the sustainability and availability of products for which demands is low. Ideally the portfolio would be achieved through collaborative agreements with productive neighboring countries.

**The Production of generic drugs**

**India's pharmaceutical industry and its ability to produce ARV drugs**

Pharmaceutical companies and foreign governments have criticized the development of India's pharmaceutical industry, as it is based on the generic reproduction of brand name products (Koshy, 1995). The Indian Patent Act, created in 1970, accounted for process patents although it did not include the patenting of products, which is said to have been controversial as this type of patenting was rare (Agrawal & Saibaba, 2001). This Act enabled Indian companies to replicate drugs that had recently begun to be sold in international markets and sell them domestically at a significantly lower cost than patented drugs sold in the developed world. Indian generic drugs usually entered the market shortly after the patented versions through a process of reverse engineering rather than innovation (2011).

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1 Infrastructure requirements for factories that produce ARVS according to Eloan dos Santos Pinheiro, consultant on ARV Development and Public Health in Brazil (2014)
Indian manufacturers of generic antiretroviral (ARV) medicines facilitated the rapid scale up of HIV/AIDS treatment in developing countries though provision of low-priced, quality-assured medicines. The legal framework in India that facilitated such production, however, is changing with implementation of the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights, and intellectual property measures being discussed in regional and bilateral free trade agreement negotiations. Reliable quantitative estimates of the Indian role in generic global ARV supply are needed to understand potential impacts of such measures on HIV/AIDS treatment in developing countries.

**Countries reporting purchase of Indian-produced generics ARVs**

![Map of countries reporting purchase of Indian-produced generics ARVs](image)

Overview of the Main Results

Differential pricing is necessary and feasible

By differential pricing is meant the adaptation of prices charged by the seller to the purchasing power of governments and households in different countries.

Economic feasibility

It was explained that differential pricing can be feasible where there are substantial fixed costs, and variable or marginal costs of production are relatively low. While there is perhaps greater scope where patented products are concerned, because of the high level of sunk R&D costs, differential pricing can also be feasible for non-patented products. Some leading economists explained how differential pricing can be in the interests of both consumers in poor countries and manufacturers, while not adversely affecting consumers in richer countries, provided markets can be effectively segmented. This entails prevention of diversion of low-priced products into high-income markets (a technical issue) and a readiness on the part of consumers in such markets to accept sustained price differences (a political issue). They also showed how differential pricing can help reconcile the twin objectives of affordability of existing essential drugs and providing incentives for research and development into new drugs, by support for R&D costs being shared according to ability to pay.

Differential pricing is already practiced, but in a limited manner

Several manufacturers already, independently of each other, offer heavily discounted prices and donations to certain poor countries for selected drugs. Experience with vaccines, contraceptives and drugs for tuberculosis shows that low prices can be made available for poor countries, both for patented and non-patented products. Reductions of 90 per cent or more below developed country prices have been achieved through bulk purchasing, competitive tenders and skillful negotiation. Therefore, generic competition can also bring prices down.
Political Feasibility

Some felt that this required political leadership, advocacy efforts and public education. Part of this will be the need to reassure public opinion that lower prices in poor countries do not mean higher prices in rich ones or a greater burden on national health budgets. Also, consideration must be given to whether differentially priced products may be seen as a form of unfair competition by local industries in developing countries and possibly subject to recourse to anti-dumping relief.

Pharmaceutical production occurs at three levels:

1. **The primary level** includes the manufacture of active pharmaceutical ingredients and intermediates from basic chemical and biological substances.
2. **Secondary production** includes the production of finished dosage forms from raw materials and excipients.
3. **The tertiary level** is limited to packaging and labeling of finished products or repackaging of bulk finished products.

Out of the 46 countries in the WHO-African Region¹, 37 have pharmaceutical industries, of them 34 have secondary level production and 25 have tertiary production. Only South Africa has limited primary production. Nine countries have no production capacity.

However, Many countries in the continent rely mainly on India and in less measure on China for imports of affordable generics and raw materials.

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¹ The World Health Organization (WHO) African Region is formed by all countries of the continent except Morocco, Tunisia, Libya, Egypt, Sudan and Somalia that belong to the WHO-Eastern Mediterranean region.
Discussion of the Results

Affordability, Availability and Accessibility

Developing countries have several international trade law provisions at their disposal to help them buy life-saving medicines at affordable prices for public health needs, particularly HIV/AIDS. But only a few countries are using these because of red tape and political pressure.

Universal access was adopted at the High-Level Meeting on HIV/AIDS in 2006 as a commitment to scale up national programs for HIV treatment, prevention, care and support for all those who need it. While clearly an ambitious and desirable goal, universal access is also a concrete process driven by countries that have organized national consultations to identify critical obstacles to scaling up, and planned measures to address these. Universal access encompasses the principles of equality, sustainability, comprehensiveness, accessibility and sustainability, which guide the development of interventions in the comprehensive package.

These must:

- Be physically accessible (geographically distributed, e.g. available not only in major cities or unavailable in hard-to-reach locations such as prisons);
- Be affordable (cost at the point of service should not be a barrier, e.g. patients should not have to pay for their treatment);
- Be equitable and non-discriminatory (there should be no exclusion criteria except medical ones, e.g. OST should not be limited to only those IDUs who are HIV-infected or who have failed on other drug dependence treatment);
- Be non-rationed (supply should be determined by need and not limited by cost or other considerations, e.g. NSPs with strict limits on the number of syringes provided to each client are less successful than those that do not impose such restrictions). Access should not be restricted by socio-demographic or other criteria such as the following:
  - Age: programs should not have age restrictions, i.e. there should be no minimum age requirement for accessing services
  - Sex/gender, sexual orientation and sexual behavior
- Citizenship, nationality, country of origin, race/ethnicity, asylum-seeking status, or religion/religious convictions
- Employment status and profession, including sex work, illegal employment, etc.
- Confinement to a facility/setting, imprisonment, military service, health institution, orphanage, etc.
- Health insurance status
- Substance use status – for example, current injecting should not be a barrier to access. In addition, all interventions should be offered voluntarily in an enabling environment created by supportive legislation, policies and strategies.

HIV/AIDS must be recognized as a problem that requires a constant supply of resources, as various organizations note (PEPFAR, 2012; UNAIDS, 2012). Increasing permanent access to ARVs is a necessary element to respond this disease.

Access to ARVs is a multidimensional issue that must be looked at from several levels. In order for medications to reach the hands of patients, proper and adequate health care must be in place, where CD4 count testing can occur, and where trained medical professionals can distribute the drugs to patients in the proper dosage. Supply chains must be fully functional, organized, and transparent to ensure the drugs arrive to a given site on time, in the correct amount, and for the accurate price.

Affordability is a key concern of European donors who finance antiretroviral drugs (ARVs) to treat AIDS in Sub-Saharan African countries. Generics are a volume-based market, relying on economies of scale. The ability of Sub-Saharan African countries to reduce their prices below large-scale manufacturers in India is challenging. In many countries in Africa, manufacturing ARV drugs could favorably affect ARV access through increased affordability;
One of the barriers to ARV price in high prevalence HIV/AIDS countries is the World Trade Organization’s Agreement on the Trade Related Aspects of Intellectual Property (TRIPS). In exchange for international trade liberalization, TRIPS requires twenty years of pharmaceutical patent protection. This provides a market monopoly for patent holding drug companies and enables them to set their prices freely. ARV prices are often out of reach for developing and least-developed countries.

WHO recommends, and donors require, international competitive tenders to ensure the lowest cost ARVs are procured. Here, razor-thin margins and large volumes are required to remain competitive. The WHO promotes the ‘rule-of-five’ which states that five bids on a tender engage enough competition to ensure the lowest generic price. Competition facilitates greater affordability by pushing prices down to marginal costs, but it is difficult for new manufacturers to match the price of longstanding firms.

**ARV Generics**

Generics markets for newer ARV regimens have not yet matured, as demonstrated by high prices, small numbers of manufacturers, and only a few three in one FDCs.

In the absence of measures to decrease drug prices and/or increase funding, countries may be forced to choose between treating fewer people with newer and “better” regimens or treating more people with older and “less desirable” regimens.

To date, generic competition has been the only proven method to promote sustained and substantial price reduction in Africa, since no manufacturer has met the standards of the WHO. However, implementation of the TRIPS Agreement in developing countries means that medicines patents are becoming more widespread and severely restricting or eliminating generic competition for newer ARVs.

Such patents could severely restrict or eliminate generic competition. Least developed countries, however, have a waiver from TRIPS obligations on pharmaceutical patents and data protection until 2016.
Local Production

Providing a local source of ARVs enhances the country's self-sufficiency for the supply of essential medications. As well, the local production of ARVs has the ability to lower the prices of the drugs, and raise treatment numbers, as domestically producing medications can lead to significant reductions in import costs (Guimier, Lee, & Grupper, 2014).

Additionally, these medicines must meet WHO prequalification standards. While the cost of second-line ARVs remains a concern, donors should focus resources on other components ARV access, such as the supply of human resources for health, health infrastructure and issues of sustainable financing.

Benefits of local production

The lack of access to basic generic medicines is a good reason to produce local medicines and to be less dependent from other countries. Local production can facilitate access to medicines for those in need.

Most Africans have no health insurance, so either the government buys and imports the drugs from foreign companies to distribute them in the national health system; or the patient has to pay from his own pocket.

A series of benefits are expected as a result of local production: save of foreign exchange; creation of jobs; increase of exports; technology transfer; raw materials produced locally will be cheaper; improvement of self-sufficiency in drug supply. Local manufacturing makes ARVs cheaper, accessible to more people, thus resulting in significant savings for the government's treatment programs.
Difficulties in the path to production

A series of blockages make difficult the production and the selling of medicines produced in Africa: heavy taxation, lack of access to inputs and raw materials, strong competition from foreign laboratories, lack of research and development, a proven system of pharmacovigilance\(^1\) and qualified human resources.

These factors are sometimes responsible of pharmaceutical production behind in Africa.

Patent and Intellectual Property Rights

To help Africa produce its own drugs, it is urgent to remove the barriers of intellectual property\(^2\), which block the rapid spread of cheap versions of existing life-saving drugs. Specific provisions of international law already exist. The flexibilities within the Trade and Related Aspects of Intellectual Property Rights (TRIPS) and DOHA Declaration on TRIPS and Public Health allow for "compulsory licensing". This means that a country for reasons of public health can lift the patent on certain drugs, provided royalties on the sale of the generic versions are paid to the laboratory that owns the patent.

Infrastructure

Unreliable water and electricity supplies, difficulties of transport, the need to import machinery, packaging, and active pharmaceutical ingredients (APIs) result of a weak chemical production in many African countries are constant difficulties that that contribute to making the product more expensive.

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1 Pharmacovigilance is the practice of monitoring the effects of medical drugs after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions.

2 Patents and intellectual property restrictions continue to affect access to antiretroviral drugs, particularly in middle-income settings, according to research presented at the 19\(^{th}\) International AIDS Conference (AIDS 2012) in Washington DC on July 25.
Quality
The big challenge is to produce high quality drugs. The operating environment can be difficult and the weaknesses at plant level in reaching and maintaining quality standards in line with established international standards (WHO) could be hard.

Legislation
The lack of regulation and of clear political will does not allow an investment security. The pharmaceutical sector lacks effective support functions among others by regulatory authorities and quality control labs.

Small domestic markets.
In Africa markets are small because the countries are small and the many in the population do not have the means of buying the medicines. The small size of domestic markets diminishes the prospects for achieving optimal production efficacy.
Limitations

My study captures only donor-funded purchases and those made by government-funded HIV/AIDS treatment program. Similarly, I had no access to comprehensive and reliable data on patents and other intellectual property barriers and was, therefore, unable to quantitatively examine these issues in my study. While I systematically cleaned and validated all transactional data, I cannot be confident that I have identified all reporting errors in publicly available data.

Prices are inconsistently reported to the Global Fund and the WHO Global Price Reporting Mechanism. Whereas some organizations, such as UNITAID and the Supply Chain Management System arm of the United States President’s Emergency Plan for AIDS Relief, provide prices for drug costs only, Global Fund-supported countries often report prices that include not only drug costs, but also add-on costs, such as transport, insurance and taxes.

I attribute ARV price reduction primarily to generic competition, but I note that these price decreases were also spurred through the efforts of HIV/AIDS activists, civil society organizations, national governments, foundations and other international organizations. Despite these limitations, my research provides valuable quantitative/qualitative information demonstrating, first, the critical role that Indian generic pharmaceutical manufacturers play in the global treatment of HIV/AIDS in developing countries, then, the benefits of a domestic production of ARVs.
Conclusions

This thesis has discussed the requisite component of increasing access of ARVS in Sub-Saharan Africa while highlighting the obstacles associates with such an enormous task.

In response to the research questions, the findings show that it is possible to lower the price of ARVs and increase its accessibility in Sub-Saharan Africa. Despite the obstacles, a local production will expand the accessibility of the drugs and drastically lower their prices. The several obstacles that African countries will or have encounter(ed) when attempting a domestic production are the challenges of:

- Obtaining a donor country quality assurance certifications,
- Limitations of the government health sector to provide treatment
- Distribution, due to the lack of infrastructure
- Availability of skilled personnel
- Rivalry between countries that might lead to limited partnerships
- Occasional wars
- Adequate regulatory environment
- Access to relevant technologies
- Achieving economies of scale

Also, Generic production is able to lower the cost of drugs, since it does not have to carry the large research and development (R&D) costs of the drug discovery process. Within the WHO framework, local manufacture is assumed to predominantly have an impact on the affordability of drugs. This in turn improves the cost-effectiveness of ARV therapy; frees resources to increase treatment numbers; and strengthens other access components. The link between domestic production and access, however, relies on two conditions:

- that these medicines can be manufactured more cheaply than they can be imported; and
- that they will meet WHO prequalification standards required for donor financing
With efforts from AIDS advocates and international organizations, such as the William J Clinton Foundation and MSF, India’s generic firms paved the way for dramatic ARV price reduction and now act as the major suppliers for developing countries. This occurred concurrently with the development of domestic manufacture in Brazil and Thailand, while in South Africa, the excessive pricing complaint brought before the Competition Commission led to the first voluntary ARV licenses under reasonable royalty terms in a developing country.

Price reduction of medicines is complex in limited-competition environments. The use of a Partnership for Productive Development Agreement as a strategy to increase the capacity of local production and to reduce prices raises issues regarding its effectiveness in reducing prices and to overcome patent barriers. Investments in research and development that can stimulate technological accumulation should be considered by the Government to strengthen its bargaining power to negotiate medicines prices under a monopoly situation.

Brazil and Thailand have been noteworthy in their efforts to reduce the prices of patent holding drug firms. In both countries, compulsory-licensing threats initiated significant price negotiations with multinationals. This, along with generic production of ARVs that were not patented domestically prior to TRIPS, facilitated a more affordable scale up in treatment. India also made use of the TRIPS Agreement’s 2006 developing country transition period. By waiting to enforce product patents in its domestic legislation, India fostered and expanded its generic drug industry. Following these initiatives, a number of Sub-Saharan African countries with substantial populations of infected people (South Africa, Zimbabwe, Zambia, Tanzania, Uganda, Kenya, and Ethiopia) are reported to be trying to manufacture ARVs domestically.
Recommendations

Local drug manufacture: Manufacturing ARVs locally could reduce the cost of HIV treatment as well as reduce the frequency of stock-out of critical ARVs

Promoting local production for ARVs in Sub-Saharan Africa

In order to maximize ARV treatment access through affordable pricing, tenders must seek the lowest cost quality drugs available. This is typically the system in place in Sub-Saharan African countries as donors stipulate international competitive tenders to procure ARVs.

The success of local manufacturers then relies on the capacity of the firm to achieve two necessary components of donor-financed tenders: international quality standards and economies of scale to lower price. The targeted financial support from the European Commission has resulted in only one grant of which we are aware and its position on the use of TRIPS safeguards to promote generic manufacturing appears contradictory. I believe that local manufacture in Sub-Saharan Africa, under current constraints, is difficult to achieve successfully.

It is not presently in the interest of patients, the governments of their countries, donors or drug companies. Consideration has and should be taken to develop regional cooperation among DRAs and manufacturers to shorten the time to market authorization and to pool procurement volumes to increase economies of scale, respectively. Politically, however, an initiative of this type seems unlikely.
Manufacturing is not solely an issue of access, but also economic development. It must address issues of financing, technology, employment, self-sufficiency, and revenue requiring policies that are difficult for a region to agree upon.

Additionally, of particular note to donor countries is that financing drug procurement and encouraging local production efforts fails to address many other critical components of the WHO access framework that prevent affordable medicines from reaching patients. Increased donor attention should address shortages of human resources, patient adherence and sustainability of pledged donor financing. While increasing the number of people receiving treatment is a short-term goal that provides impressive statistics, it neither addresses sustainability nor does it improve the fragmented health system and poor health infrastructure.
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Appendix

Figure 1: Problem Analysis Diagram Of Factors Contributing To Non-Adherence To ARVs

SERVICE FACTORS
- Poor support services
  - Inadequate trained health workers
  - Treatment guidelines not available
  - Poor drug supply
  - Insufficient infrastructure

DISEASE AND TREATMENT FACTORS
- Seriousness of the disease
- Side effects + ADRs
- Pill burden

SOCIO-ECONOMIC AND CULTURAL FACTORS
- Beliefs and patient’s preference to traditional medicines and alternative therapy
- Perception on the causes and transmission of HIV
- Religion
- Poor patient knowledge, information
- Negative perception on treatment
- Age, sex, literacy level of patient
- Poor social support
- Stigma in the community and health workers
- Lack of employer support
- Occupation
- Mobility
- Cost of treatment
- Poverty

NON ADHERENCE TO ARVs
- Long distance to the health facility
- Long waiting time

Source: UNAIDS, Report 2014
Source: UNAIDS, Report 2016

Distribution of new adult HIV infections and population by age and sex, global and in sub-Saharan Africa, 2015

Source: UNAIDS 2016 estimates.
Facts on Antiretrovirals

What is an Antiretroviral Therapy?

Standard antiretroviral therapy (ART) consists of the combination of antiretroviral (ARV) drugs to maximally suppress the HIV virus and stop the progression of HIV disease. ART also prevents onward transmission of HIV. Huge reductions have been seen in rates of death and infections when use is made of a potent ARV regimen, particularly in early stages of the disease. The World Health Organization recommends ART for all people with HIV as soon as possible after diagnosis without any restrictions of CD4 counts. It also recommends offer of pre-exposure prophylaxis to people at substantial risk of HIV infection as an additional prevention choice as part of comprehensive prevention. Countries are now following to adapt and implement these recommendations within own epidemiological settings.

What is the HIV Life Cycle?

There are several steps in the HIV life cycle:

1. Free virus circulates in the bloodstream
2. HIV attaches to a cell
3. HIV empties its contents into the cell
4. The HIV genetic material (RNA) is used by the reverse transcriptase enzyme to build HIV DNA
5. The HIV DNA is inserted into the cell’s chromosome by the HIV integrase enzyme. This establishes the HIV infection in the cell
6. When the infected cell reproduces, it activates the HIV DNA, which makes the raw material for new HIV viruses
7. Packets of material for a new virus come together
8. The immature virus pushes out of the infected cell in a process called “budding”
9. The immature virus breaks free of the infected cell
10. The new virus matures: raw materials are cut by the protease enzyme and assembled into a functioning virus

Approved ARV Drugs

Each type, or “class”, of ARV drugs attacks HIV in a different way. The first class of anti-HIV drugs was the **nucleoside reverse transcriptase inhibitors** (also called NRTIs or “nukes”). These drugs block step 4, where the HIV genetic material is used to create DNA from RNA.

The following drugs in this class are used:

- Zidovudine (Retrovir, AZT)
- Didanosine (Videx, Videx EC, ddI)
- Stavudine (Zerit, d4T)
- Lamivudine (Epivir, 3TC)
- Abacavir (Ziagen, ABC)
- Tenofovir, a nucleotide analog (Viread, TDF)
- Combivir (combination of zidovudine and lamivudine)
- Trizivir (combination of zidovudine, lamivudine and abacavir)
- Emtricitabine (Emtriva, FTC)
- Truvada (combination of emtricitabine and tenofovir)
- Epzicom (combination of abacavir and lamivudine)

**Non-nucleoside reverse transcriptase inhibitors, also called non-nukes or NNRTIs**, also block step 4 but in a different way. Five have been approved:

- Nevirapine (Viramune, NVP)
- Delavirdine (Rescriptor, DLV)
Efavirenz (Sustiva or Stocrin, EFV, also part of Atripla)
Etravirine (Intelence, ETR)
Rilpivirine (Edurant, RPV, also part of Complera or Epivlera)

**Protease inhibitors** or **PIs** block Step 10, where the raw material for new HIV virus is cut into specific pieces.

Ten protease inhibitors are approved:

**Saquinavir (Invirase, SQV)**
**Indinavir (Crixivan, IDV)**
**Ritonavir (Norvir, RTV)**
**Nelfinavir (Viracept, NFV)**
**Amprenavir (Agenerase, APV)**
**Lopinavir/ritonavir (Kaletra or Aluvia, LPV/RTV)**
**Atazanavir (Reyataz, ATZ)**
**Fosamprenavir (Lexiva, Telzir, FPV)**
**Tipranavir (Aptivus, TPV)**
**Darunavir (Prezista, DRV)**

**Entry inhibitors** prevent HIV from entering a cell by blocking step 2 of the life cycle.

Two drugs of this type have been approved:

**Enfuvirtide (Fuzeon, ENF, T-20)**
**Maraviroc (Selzentry or Celsentri, MVC)**

**HIV integrase inhibitors** prevent HIV from inserting its genetic code into the human cell’s code in step 5 of the life cycle.

The drugs of this type are:
Raltegravir (Isentress, RAL)
Elvitegravir (EVG, part of the combination Stribild)
Dolutegravir (Tivicay, DTG)

How are ARVs Used?

Antiretroviral drugs are usually used in combinations of three or more drugs from more than one class. This is called "Combination Therapy." Combination therapy helps prevent drug resistance.
Manufacturers of ARVs keep trying to make their drugs easier to take, and have combined some of them into a single tablet regimen.

What is Drug Resistance?

When HIV multiplies, many of the new copies have mutations: they are slightly different from the original virus. Some mutant viruses keep multiplying even when you are taking ARV drugs. When this happens, the virus can develop resistance to the drug and ART may stop working.

If only one or two ARV drugs are used, it is easy for the virus to develop resistance. For this reason, using just one or two drugs is not recommended. But if two or three drugs are used, a successful mutant would have to “get around” all of the drugs at the same time. Using combination therapy means that it takes much longer for resistance to develop.

Can These ARVs Cure AIDS?

ARVs reduce the viral load, the amount of virus in your bloodstream, but are not a cure. A blood test measures the viral load. People with undetectable viral loads stay healthier longer. They are also less likely to transmit HIV infection to others.

Some people’s viral load is so low that it is “undetectable” by the viral load test. This does not mean that the virus is gone, and it does not mean a person is cured of HIV infection.
**Patents of Antiretroviral**

A patent is a form of legal right granted by government to provide exclusivity over a new invention for a limited period of generally 20 years. During that period, the patent holder has the right to exclude others from making or selling the patented invention in the country (or countries) in which the patent was granted. Patents can be granted for different types of inventions, including a new medicine, such as a new ARV.

To obtain a patent on a new ARV, a pharmaceutical company or research organization must file a patent application at the national patent office of each country in which it would like to obtain exclusivity. Each patent office is then responsible for examining the application and making a decision on whether the invention described in the application fulfills the criteria for patentability. The patent examination process generally takes several years and during that period the patent application is considered to be pending. If the invention is considered to meet the patentability criteria, the patent office grants a patent which confers exclusive rights on the patent holder, thus effectively enabling the patent holder to prevent others from making, selling or using the patented product or process in the country for which the patent was granted.

Some patent offices provide opportunities for third parties to submit patent oppositions during a specified period of time. Depending on national laws, this may happen prior to the grant of a patent or after a patent has been granted. Patents may be granted for new products such as medicines, or for processes for manufacturing those medicines. Product patents may be granted on new molecules (often referred to as “base” patents or “compound” patents), or on specific forms or formulations of medicines (often referred to as “secondary” patents). The latter could include, for example, a particular salt form, an oral solution or tablet formulation of a given medicine, or a fixed-dose combination that combines more than one ARV compound into a single pill. Some secondary patents (notably those related to liquid dosage forms) are relevant to pediatric formulations of a medicine but do not cover formulations for adults.
In practice, new ARVs are generally covered by more than one patent or patent application. In certain instances, information on several secondary patents on the same ARV has been combined for the sake of simplicity. This is notably the case for combination products or where there are multiple secondary patents/patent applications on a particular ARV. In such cases, the text and tables indicate whether at least one secondary patent has been granted, and if not whether at least one application was filed.

**Patents As Territorial Rights**

Patents are territorial rights, which means that they have effect only in the specific territory for which they were granted. Usually the territory is a country, but there are also some regional patent offices that grant patents for a group of countries. For instance, this is the case of the OAPI, which grants patents that are valid in 16 countries in Africa. Other regional patent offices that are referred to in this thesis are the ARIPPO and the EAPO.

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

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