

Understanding Patent Pools for Global Health: Assessing Their Value in Promoting  
Access to Essential Medicines

by

Ashley Eisenberg

Duke Global Health Institute  
Duke University

Date: \_\_\_\_\_

Approved:

\_\_\_\_\_  
Randall Kramer, Co-Supervisor

\_\_\_\_\_  
Anthony So, Co-Supervisor

\_\_\_\_\_  
Jerome Reichman

Thesis submitted in partial fulfillment of  
the requirements for the degree of  
Master of Science at the Duke Global Health Institute  
of Duke University

2014

ABSTRACT

Understanding Patent Pools for Global Health: Assessing their Value in Promoting

Access to Essential Medicines

by

Ashley Eisenberg

Duke Global Health Institute  
Duke University

Date: \_\_\_\_\_

Approved:

\_\_\_\_\_  
Randall Kramer, Co-Supervisor

\_\_\_\_\_  
Anthony So, Co-Supervisor

\_\_\_\_\_  
Jerome Reichman

An abstract of a thesis submitted in partial  
fulfillment of the requirements for the degree  
of Master of Science at the Duke Global Health Institute of  
Duke University

2014

Copyright by  
Ashley Eisenberg  
2014

## **Abstract**

In response to a lack of access to essential medicines in the developing world, a number of mechanisms have developed that aim to promote greater access to essential medicines, particularly antiretroviral drugs for the treatment of HIV/AIDS and drugs for the treatment of neglected diseases. These mechanisms operate in a variety of different ways, but share a common theme in that they all ultimately aim to provide greater access to affordable drugs to patients in resource-poor settings. However, the existing mechanisms to facilitate increased access to essential medicines, while beneficial, all have a number of cons. Patent pools represent a novel approach to facilitating access to essential medicines and have the potential to go beyond the status quo as compared to various traditional alternatives.

This paper aims to analyze patent pools recently formed in the field of global health and whether such approaches to intellectual property management can facilitate greater access to antiretroviral medicines for the treatment of HIV/AIDS and drugs for the treatment of neglected diseases in low- and middle-income countries, both in terms of fostering the developing of new drugs and increasing the affordability and availability of drugs current in the market. Two patent pools in particular—the Medicines Patent Pool and WIPO’s Re:Search Consortium—are evaluated and compared to existing mechanisms that aim to accomplish the same or similar goals.

## **Dedication**

To all those living in low- and middle-income countries without access medical care, in hopes that the information presented in this thesis will increase awareness of your struggle.

# Contents

Abstract.....	iv
List of Tables .....	ix
List of Figures .....	x
List of Abbreviations .....	xi
Acknowledgements .....	xiii
1. Introduction .....	1
1.1 Access to Essential Medicines in the Developing World.....	1
1.2 The Present HIV/AIDS Situation in LMICs .....	5
1.3 Neglected Disease Situation in LMICs .....	8
2. IP Barriers to Access to Medicine .....	11
2.1 Overview of IP, TRIPS, and the Doha Declaration.....	11
2.2 IP Barriers to ARVs .....	16
2.2.1 India’s Role in Access to ARVs in LMICs .....	19
2.3 Barriers to ND Research .....	21
2.3.1 The Potential Role for India and other Emerging Economies in ND R&D.....	24
3. Overview of Mechanisms to Facilitate Broader Access to Medicines .....	26
3.1 Facilitating Access to ARVs .....	26
3.2 Facilitating Access to ND Drugs .....	27
3.3 Overview of Patent Pools for Global Health .....	28
3.3.1 Patent Pools Generally.....	28

3.3.2 Patent Pools for Global Health .....	29
4. Traditional Mechanisms that Facilitate Access to ARVs.....	32
4.1 Voluntary Licensing .....	32
4.2 Compulsory Licensing.....	36
4.2.1 Compulsory Licenses in Thailand .....	39
4.3 Non-Assert Declarations .....	42
4.4 Drug Donations .....	45
4.5 Tiered/Differential Pricing .....	48
5. The Medicines Patent Pool: A Novel Approach for Increasing Access to ARVs .....	52
5.1 History and Overview of the MPP.....	52
5.2 Theoretical Benefits of MPP .....	54
5.3 MPP Engagement .....	57
6. Overview of Current MPP Licenses .....	59
6.1 NIH License.....	59
6.2 Gilead Sciences License .....	59
6.3 ViiV Healthcare License for Pediatric ABC .....	65
6.4 Roche Agreement .....	69
6.5 Bristol-Myers Squibb License .....	72
6.6 ViiV Healthcare License for DTG for Adult and Pediatric Use and ABC for Adult Use .....	76
7. Comparison of the MPP to Traditional Alternatives.....	82
8. Is the MPP better than the Alternatives? .....	86

9. R&D Efforts for NDs.....	90
9.1 The ND R&D Landscape .....	90
9.2 ND R&D Collaborations.....	93
9.2.1 Product Development Partnerships .....	93
9.2.2 Other ND R&D Collaborations .....	98
10. WIPO Re:Search Consortium .....	100
10.1 History of WIPO Re:Search.....	100
10.2 Overview of Re:Search.....	102
10.3 Theoretical Benefits of Re:Search .....	105
10.4 Re:Search so Far .....	108
11. Does Re:Search Make a Positive Difference in Facilitating ND R&D?.....	111
12. Conclusion.....	113
Appendix A: Voluntary Licenses.....	115
Appendix B: Countries Eligible for Pharmaceutical Company Price Discounts .....	118
Appendix C: Comparison of MPP Licenses .....	122
Appendix D: Comparison of MPP-Gilead License to 2006 Gilead Voluntary Licenses for TDF .....	126
Appendix E: Private Sector ND R&D Facilities .....	127
Appendix F: Re:Search Collaboration Agreements .....	128
References.....	134



## List of Tables

Table 1: Percentage of Global Neglected Disease R&D Funding.....	85
Table 2: Various PDPs, with Disease and Product Focus.....	88
Table 3: Contributions to the Re:Search Database.....	114

## List of Figures

Figure 1: Price Comparison of First-Line, Second-Line, and Possible Third-Line Treatment Regimens.....	6
Figure 2: Generic Competition as a Catalyst for Price Reductions.....	17

## List of Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
NDs	Neglected Diseases
FDCs	Fixed-Dose Combinations
ARVs	Antiretrovirals
LMICs	Low- and Middle-Income Countries
IP	Intellectual Property
R&D	Research and Development
MICs	Middle-Income Countries
WHO	World Health Organization
NTDs	Neglected Tropical Diseases
WTO	World Trade Organization
TRIPS	Agreement on Trade Related Aspects of Intellectual Property
LDCs	Least Developed Countries
CL	Compulsory License
FTA	Free Trade Agreement
TB	Tuberculosis
PDP	Product Development Partnership
MPP	Medicines Patent Pool
API	Active Pharmaceutical Ingredient
MOU	Memorandum of Understanding
BMS	Bristol Myers Squibb
FTC	Emtricitabine
TDF	Tenofovir
EVG	Elvitegravir
COBI	Cobicistat
FDA	Food and Drug Administration
ABC	Abacavir
3TC	Lamivudine
DTG	Dolutegravir
CMV	Cytomegalovirus
LPV	Lopinavir
LPV/r	Lopinavir/Ritonavir
NPV	Nevirapine
RTV	Ritonavir
SQV	Saquinavir
ATV	Atazanavir

RTV Ritonavir  
NGO Non-Governmental Organization  
NIH National Institutes of Health  
WIPO World Intellectual Property Organization  
BVGH BioVentures for Global Health  
MSF Medecins Sans Frontieres

## Acknowledgements

I would like to express my deepest gratitude to my thesis committee, Randall Kramer, Dr. Anthony So, and Jerome Reichman. Anthony, thank you for spending so many hours working with me and challenging me to put together the best work possible. Without the support, guidance, and advice of all of you, this thesis would not have been possible. I am honored to have had the ability to work with all of you, and your brilliance continues to amaze and inspire me everyday.

To Jason Cross, thank you for your mentorship for the past three years. The countless hours you have spent working with me throughout my time at Duke have been instrumental in shaping my interests and this thesis. Your mentorship has been an invaluable part of shaping my career goals and my interest in the access to medicine field, and I will be forever grateful for your guidance and support.

I would also like to thank Sarah Martin for her continuing support throughout my time at Duke and for granting me the flexibility to successfully pursue my dual degree in alignment with my access to medicine interests.

To my family and friends, thank you for your unwavering love, support, and understanding throughout this process and my academic career. Julian Veshi, thank you for keeping me sane throughout this process and supporting me in everything I do.

# 1. Introduction

## 1.1 Access to Essential Medicines in the Developing World

Approximately one-third of the world's population lacks access to essential medicines.<sup>1</sup> This includes medicines for a range of diseases,<sup>2</sup> including those for the treatment of HIV/AIDS and neglected diseases (NDs). This is a particularly unfortunate situation because a majority of patients in need of essential medicines are afflicted by diseases that are preventable, curable, or can be managed by existing treatments that are available but to which they lack access, either because the drugs are too costly or not tailored to patients in developing countries. Others suffer from a lack of access because the medicines they need have yet not been developed.

While strong patent protection greatly contributes to patients' lack of access to essential medicines in developing countries, a number of other factors further undermine the availability of such medicines.<sup>3</sup> Some other factors contributing to the access problem include: poor infrastructure that results in delayed or inadequate supply and distribution of medicines; insufficient health facilities and staff; low investment in

---

<sup>1</sup> The WHO defines essential medicines as drugs that "satisfy the priority health care needs of the majority of the population" and should thus be available "at all times, in adequate amounts and in appropriate dosage forms."

<sup>2</sup> The WHO List of Essential Medicines includes over 350 medicines.

<sup>3</sup> It is thus important to keep in mind that, while increasing access to drugs via price reductions is a necessary component to solving the global access to medicine problem, it is not sufficient.

health by national governments; poor sanitation; legal and social barriers that prevent discriminated groups<sup>4</sup> from obtaining access to drugs; and stigma associated with disease and lack of education that negatively impact health-seeking behavior.

Despite these barriers to treatment, one of the greatest barriers is patent protection over pharmaceuticals.<sup>5</sup> Strong patent protection inhibits access to medicines for both HIV/AIDS and NDs, though the landscapes for the two are quite different.<sup>6</sup> Though low- and middle-income countries (LMICs) make up most of the disease burden of both, HIV/AIDS treatments commands a global market whereas most ND treatment does not. This difference is significant and impacts the types of solutions needed to solve the access problem for each.

With respect to HIV/AIDS, a number of treatments exist that have been proven successful at ameliorating the effects of the disease, curtailing the spread of the virus and prolonging the lives of people living with HIV/AIDS. Fixed-dose combinations (FDCs) that combine three or four different drugs are being increasingly used to treat

---

<sup>4</sup> Particularly sex workers, intravenous drug users, and men who have sex with men.

<sup>5</sup> Despite the fact that about 90% of the drugs on the WHO Essential Medicines List are off patent, the inclusion of drugs on the list is based, in addition to effectiveness and safety, on cost effectiveness. Thus, a lot of newer, patented drug are not included in the list because of high prices, but would be included if prices were lower.

<sup>6</sup> HIV/AIDS and some NDs (e.g. TB and malaria) can be classified as “Type II” diseases, meaning that they occur in both wealthy and poor nations, and thus R&D incentives exist, but the level of R&D spending is very low compared to the global disease burden. Other NDs, particularly NTDs, can be classified as “Type III” diseases, meaning they occur almost exclusively in poor countries, and thus R&D for them is almost entirely lacking.

HIV/AIDS. In addition to increased efficacy over individual drugs and decreased drug resistance, FDCs offer advantages over single-dose drugs in that they are easier to administer and distribute and increase patient adherence to treatment [1]. A country's ability to procure affordable antiretrovirals (ARVs) greatly impacts its ability to fight the epidemic because successful treatment depends on a continuous, reliable supply of ARVs. Primarily due to generic competition, the price of ARVs has dropped by more than 99% over the last decade [2].<sup>7</sup> However, the treatment needs of patients in LMICs are changing, and the number of people needing newer, better treatment is increasing. Current first-line regimens offered in LMICs<sup>8</sup>, while inexpensive due to lack of patent protection, often have many adverse side effects and can be highly toxic to patients [116]. Additionally, the incidence of drug resistance to first-line therapy is increasing in LMICs. The prevalence of drug resistance to any given ARV after eight years of treatment is, on average, 7.4%, and is increasing in certain LMICs, particularly Sub-Saharan Africa, by 14% per year [2]. This means that, at an increasing rate, newer, patented, second- and third-line ARVs will be needed in LMICs. However, because of strong patent protection, the price of newer ARVs remains extremely high in most

---

<sup>7</sup> First-line treatments today are available at just under \$100 per patient per year, as compared to the price in 2000, when first-line treatments (which were still under patent protection) were priced at \$10,000 per patient per year.

<sup>8</sup> The majority of patients in LMICs receiving first-line treatment are taking a combination of 3 drugs: 3TC, d4T, and NVP. D4T causes drastic weight loss in many patients and can cause life-threatening lactic acidosis. As a result, this treatment regimen is very rarely used in developed countries.



developing countries, where the impact of HIV/AIDS has been most devastating. While lobbying groups around the world have had some success in increasing access to these newer, patented drugs, costs still remain prohibitively high for many patients in developing countries. Thus, as current treatment regimens lose their effectiveness due to drug resistance, and as newer, less toxic, first-line treatments are needed, the ability of the fifty-five million people expected to need ARVs by 2030 [116] to access affordable treatment is being jeopardized by strong patent protection.

Strong patent protection also affects the availability of drugs for the treatment of neglected diseases because it limits access to not only patents, but data and know-how as well. Because the ND drug market is so small, most patents related to ND drugs have little or no commercial value, and thus IP holders do not have a very strong incentive to protect these patents relative to the incentives to protect patents related to profitable drugs. Thus, access to data and know-how is arguably more important than access to patents in the ND context. Those wanting to use these patents, data, and know-how to engage in research and development (R&D) and innovate new diagnostics, technologies, and drugs for NDs are prohibited from doing so because of the patents held by pharmaceutical companies on underlying basic technologies and other necessary research inputs. And because existing IP regimes create an incentive structure whereby

pharmaceuticals companies are largely driven by profit rather than health needs<sup>9</sup>, pharmaceutical companies holding this IP don't have an incentive to use it and innovate.

A situation thus emerges where R&D for NDs is seriously lacking. Because of the small demand for ND treatment, pharmaceutical companies have little incentive to invest in R&D for NDs because it is unlikely that the market exclusivity offered by patent protection will be sufficient to recoup R&D costs. Thus, the parties with access to patents have no incentive to use them, and anyone else wanting to use patents, data, and know-how relevant for ND drug development is unable to do so because of patent barriers. Because of this situation, cures for NDs either have not been developed or are not available to patients in LMICs, despite the fact that NDs make up a significant percentage of the global disease burden.

## ***1.2 The Present HIV/AIDS Situation in LMICs***

As compared to a couple decades ago, HIV today is a manageable illness but requires a lifetime of treatment. Of the thirty-five million people living with HIV/AIDS throughout the world [3], 28.6 million reside in LMICs. Since the turn of the last century, there has been a massive scale-up of treatment in LMICs. This has been largely due to the expiration of patents on first-line medicines that has allowed for robust

---

<sup>9</sup> Because NDs are virtually absent from developed nations and occur almost exclusively in LMICs where patients are largely unable to afford expensive drugs, it is difficult, if not impossible, for pharmaceutical companies to recoup their R&D costs or profit from the sale of drugs, and thus there is little or no financial incentive for pharmaceutical companies to engage in R&D for NDs.

generic competition for ARVs [4], which has dramatically reduced the price of treatment,<sup>10</sup> and for the formulation of generic FDCs,<sup>11</sup> a simplified treatment regimen that requires patients taking only two pills a day, leading to increased adherence to ARVs,<sup>12</sup> which decreases drug resistance. This scale-up has been monumentally important, not just because treatment prolongs the lives of people living with HIV, but also because it dramatically decreases transmission rates<sup>13</sup> [3].

While the massive scale-up in treatment over the last decade has resulted in 9.7 million people in LMICs currently receiving treatment [3], about nineteen million still lack access to treatment [5]. Thus, despite the great strides that have been made, only 34% of the 28.6 million people living with HIV/AIDS in LMICs are currently receiving treatment [6]. While treatment rates vary significantly by country, of all the LMICs, only nine have reported treatment coverage of greater than 80%, and sixty-eight have reported coverage of less than 50% [7].

---

<sup>10</sup> First-line treatments today are available at just under \$100 per patient per year, as compared to the price in 2000, when first-line treatments (which were still under patent protection) were priced at \$10,000 per patient per year.

<sup>11</sup> Particularly the generic first-line FDC stavudine/lamivudine/nevirapine.

<sup>12</sup> Increased adherence to treatment is significant because it decreases the incidence of drug resistance, which develops primarily in patients who take ARVs intermittently.

<sup>13</sup> For an HIV-positive individual on antiretroviral therapy, the risk of transmitting the virus is reduced by 96%.

While the cost of first-line treatment in LMICs has dropped as low as just under \$100 per patient per year for generic versions<sup>14</sup> [120]—a 16% price decrease over the past year alone [2]—second- and third-line treatments remain too expensive for most patients,<sup>15</sup> particularly in middle-income countries (MICs) that do not receive price discounts from pharmaceutical companies<sup>16</sup> [2] (see Appendix B). Out of pocket payments are still the primary source for covering the cost of medicines in LMICs [8, 117]; this means that even the cost of first-line treatments is out of reach for millions living in LMICs who survive on just \$1/day.

As first-line treatments continue to fail at greater rates due to incidence drug resistance<sup>17</sup> [4] or toxicity, an increasing number of people in LMICs need second-line treatments, the cost of which is dramatically higher than first-line treatments (Figure 1). This has created an urgent need to make affordable second-line treatments available in LMICs.

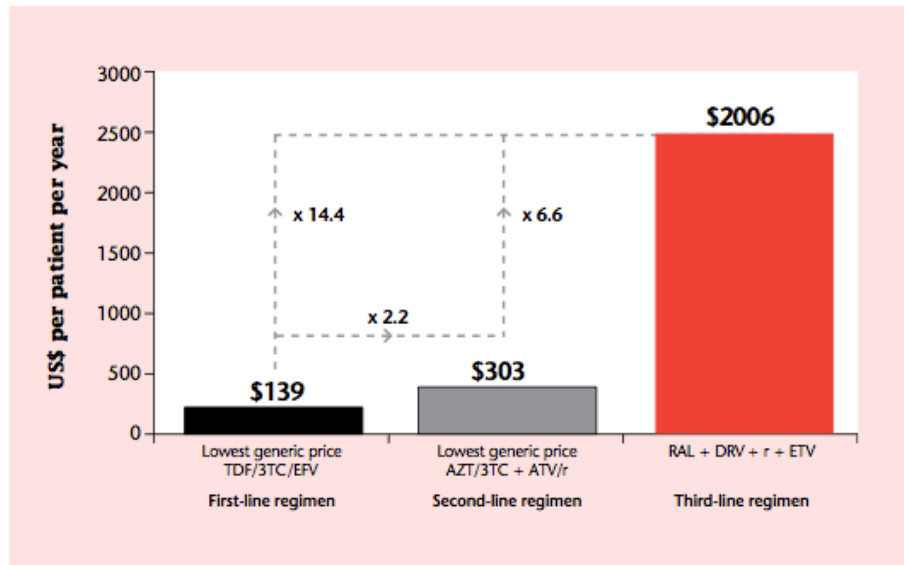
---

<sup>14</sup> Competition among generic suppliers has decreased the price of treatment from \$10,000 per patient per year in 2000 to as little as \$79 per patient per year today.

<sup>15</sup> To date, the cheapest second-line treatment available in LMICs is \$303 per patient per year, and the cheapest third-line treatment regimen available is \$2,006 per patient per year.

<sup>16</sup> For example, the ARV LPV/r (patent held by Abbott) is priced at \$265 per patient per year in qualifying “Category 1” countries, whereas LPV/r is priced in middle-income countries (which Abbott classified as “Category 2” countries) at \$740 per patient per year.

<sup>17</sup> In one study conducted in Khayelitsha, South Africa by MSF, 16% of patients on treatment for 5 years needed to be switched to second-line FDCs.



**Figure 1: Price Comparison of First-Line, Second-Line, and Possible Third-Line Treatment Regimens**

### **1.3 Neglected Disease Situation in LMICs**

Broadly speaking, neglected diseases<sup>18</sup> are those diseases that have high mortality rates in developing countries but are virtually absent in developed nations. Neglected tropical diseases (NTDs) are a subset of neglected diseases, encompassing those diseases that almost exclusively affect those living in LMICs.<sup>19</sup> The World Health Organization (WHO) estimates that one billion people (one-sixth of the world's population) currently suffer from one or more NDs [9]. However, despite this high

---

<sup>18</sup> G-FINDER classifies the follow as neglected diseases: HIV/AIDS, malaria, TB, dengue, diarrheal diseases, kinetoplastids, bacterial pneumonia & meningitis, helminth infections, salmonella infections, trachoma, leprosy, Buruli ulcer and rheumatic fever.

<sup>19</sup> The WHO classifies the follow as neglected tropical diseases: Buruli ulcer, Chagas disease, taeniasis/Cysticercosis, dengue, Dracunculiasis, Echinococcosis, endemic treponematoses, foodborne trematodiasis, human African trypanosomiasis, the Leishmaniasis, soil-transmitted helminthiasis.

disease burden, many NDs lack effective treatments because pharmaceutical R&D is primarily market driven, rather than based on health needs. There is thus little correlation between health R&D that is needed, based on burden of disease data, and that which is ultimately undertaken [10].

However, there are some NDs for which treatments exist, but many do not effectively reach those who need it, or are old,<sup>20</sup> toxic, and/or ineffective at treating patients who have developed drug resistance to these treatments [39]. Additionally, many existing treatments are not suited for use in LMICs, as they “require long-term protocols, have inconvenient administration, require refrigeration, lack available vaccines, or have low efficacy/poor safety profiles and serious side effects” [11]. There are also some treatments available in the form of drugs that have been developed for developed-country markets but have proven to be simultaneously effective in treating NDs<sup>21</sup> [12]. For the few NDs that have small developed-country markets (e.g. Chagas disease, TB, malaria), some treatments have been developed, but these treatments often are not adapted to treat patients in LMICs because they are expensive and/or difficult to administer.

---

<sup>20</sup> Many ND treatments have not been updated since the early 20<sup>th</sup> century. For example, the TB vaccine that has not been updated since 1924 and the primary first-line drug regimen for TB was developed in the 1960s.

<sup>21</sup> For example, amphotericin B, originally developed as an antifungal drug sold in developed countries, is also useful for the treatment of leishmaniasis. Eflornithine (developed as an anti-facial hair treatment) is also an effective treatment for HAT.

Despite the availability of some treatments, the global disease burden for NIDs remains high, with many lacking treatment altogether. The high global burden of NIDs has created an urgent need to incentivize R&D in this area, and a number of mechanisms have developed with this aim. However, because NIDs are virtually absent from developed nations, there is little investment in R&D for new vaccines and treatments aimed at combatting these diseases. Being almost exclusively prevalent in LMICs, most of the patients who need the drugs are not able to afford them, making it difficult, if not impossible, for pharmaceutical companies to recoup their R&D costs or profit from the sale of drugs. There is thus little or no financial incentive for pharmaceutical companies to engage in R&D for NIDs, resulting in a lack of viable treatment options available to those living in LMICs. This has created an urgent need to come up with innovative models that can increase NID R&D and ultimately lead to the development of drugs that are inexpensive, easy to administer, and tailored to patients in LMICs.

## **2. IP Barriers to Access to Medicine**

### ***2.1 Overview of IP, TRIPS, and the Doha Declaration***

All countries that are members of the World Trade Organization (WTO) are required to grant drug patents to pharmaceutical companies, pursuant to the 1994 WTO Agreement on Trade Related Aspects of Intellectual Property (TRIPS)<sup>1</sup> [13]. TRIPS sets out minimum international standards regarding intellectual property (IP) protection with which all member countries must comply. Specifically with regard to patents, TRIPS requires that member countries structure their national patent laws so that eligible patent holders of drugs are granted a monopoly in the marketplace, allowing them to prevent others from making, using, selling, or importing the drug<sup>2</sup> for the duration of the patent—twenty years from the filing of the patent minus the time necessary to evaluate the patent<sup>3</sup> [13]. By removing generic competition from the marketplace, which serves as a major catalyst for price reductions of drugs [2], pharmaceutical companies holding patents are able to charge astronomically high prices for drugs—prices that are out of reach for most in the developing world.

---

<sup>1</sup> See Article 27(1) of TRIPS.

<sup>2</sup> See Article 27 of TRIPS.

<sup>3</sup> See Article 33 of TRIPS.



The strong patent protection on pharmaceuticals that is required by TRIPS has been quite controversial and has garnered a lot of international criticism. One such criticism is that TRIPS “was the product of duress by powerful states against weak states rather than a bargain struck by sovereign equals” [14], effectuated through the threat of trade sanctions and the promise of better trade access. As such, the protections provided by TRIPS tend to be much more favorable to developed nations—since developed nations hold over 80% of the world’s drug patents [15], they reap the benefits of strong IP protection much more than developing countries. Proponents of strong international IP protection claim that such protection necessary to ensure that pharmaceutical companies recoup the R&D costs associated with bringing a drug to the market, which is necessary for future innovation [16]. However, there has been much debate over whether such strong IP protection is actually necessary to recoup R&D costs. In some cases, due to a lack of transparency, it is unclear how much money is actually spent on R&D by pharmaceutical companies and how much is funded by national governments<sup>4</sup> [17, 118]. It is also unclear how much money is spent on marketing new drugs, which is often included under the umbrella of R&D costs; some

---

<sup>4</sup> A number of drugs developed by private pharmaceutical companies in the United States are heavily funded by the National Institutes of Health. An example of this is the Abbott’s HIV drug Ritonavir. Though the NIH heavily funded the R&D for the drug, prices remained as high as they would for any other drug. Additionally, a study by Stevens et al. examining the role of public-sector research in the discovery of drugs and vaccines found that, from 1990-2007, public-sector research institutions have contributed to the discovery of 9.3-21.2% of all drugs involved in new-drug applications approved.

estimates suggest that about one-third of all sales revenue is actually spent on marketing new products—roughly twice what is spent on R&D [18]. Proponents of strong IP protection also claim that it could serve as “a powerful tool for development” [19], ultimately resulting in the availability of new and improved medicines in developing countries.

Unfortunately, rather than bringing about such development, strong patent protection has acted as a huge barrier to access to medicine in the developing world, where resources are limited and the cost of improved quality drugs remains largely unaffordable [20]. The 2001 Doha Declaration on the TRIPS Agreement and Public Health spoke directly to this issue [21]. It acknowledged the “gravity of the public health problems affecting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria, and other epidemics”<sup>5</sup> [21] and emphasized that the “TRIPS agreement does not and should not prevent Members from taking measures to protect public health”<sup>6</sup> [21]. In essence, the Doha Declaration affirmed the right of countries, particularly in the developing world, to take advantage of flexibilities contained within TRIPS in order to promote access to essential medicines in light of public health needs.

---

<sup>5</sup> See §1 of the Doha Declaration.

<sup>6</sup> See §4 of the Doha Declaration.

The Doha Declaration was monumental in its recognition that countries in the developing world need ways to procure affordable medicines. However, TRIPS also recognized this, albeit less explicitly, when it allowed for a transition period that permitted developing and least-developed countries (LDCs) to delay full compliance with TRIPS [13]. By creating different compliance timelines for countries at different stages of development, developing and least-developed countries were able to delay full compliance until 2005 and 2021, respectively<sup>7</sup> [22]. Because of these different compliance timelines, LDCs are still exempt from granting patent protection to pharmaceutical companies and are granted maximum flexibility to produce and distribute medicines. Unfortunately, a number of LDCs have failed to take full advantage of the compliance extension and already grant pharmaceutical patents, often as a result of trade pressure from developed nations. For example, by 2004, twenty-eight of the thirty least-developed African countries already had adopted patent laws [23].

Despite the strong patent protection required by TRIPS, patent protection under TRIPS is not limitless, even within the twenty-year period of patent protection. Espoused in TRIPS and affirmed by the Doha Declaration are a number of flexibilities that developing countries can and should take advantage of to promote access to

---

<sup>7</sup> LDCs were initially given 10 years to become fully TRIPs compliant, but in 2005 this grace period was extended until 2013 for most IP protections and 2016 for patent protection of pharmaceuticals. The grace period was extended again in October 2013 until July 1, 2021 (or until a particular country ceases being classified as a LDC).

medicine. One such flexibility that has been taken advantage of by developing countries is the right to issue compulsory licenses (CLs)<sup>8</sup> [13], which permit a nation, or third party authorized by that nation, to use a patented invention without the permission of the patent holder in exchange for payment of a government-determined royalty [24]. This important exception to a patent holder's right to exclusivity, though controversial and seldom used in the past<sup>9</sup> [23], has, in recent years, been increasingly used by developing countries and has been extremely influential in promoting access to medicine.

In addition to the strong patent protection over pharmaceuticals mandated by TRIPS, there are other regimes affecting access to medicine in developing countries, particularly free trade agreements (FTAs) between developing and developed countries that require developing countries to enact national patent laws that go above and beyond what is required by TRIPS, known as "TRIPS-Plus" provisions. Many FTAs, for example, require countries to adopt data exclusivity laws that serve to extend a company's patent term beyond twenty years by restricting the ability of generic manufacturers to use previous clinical trial data for a period of time to show a bioequivalent generic's efficacy [26]. These laws create additional market entry barriers and further hamper the development of generics because clinical trials can be expensive. Thus, many generic companies may choose to wait out the data exclusivity period rather

---

<sup>8</sup> See Article 31 of TRIPS.

<sup>9</sup> In 2003, "compulsory licensing is so extraordinarily rare that it has not been used once in the last decade by any country in respect to a finished medicine."

than conducting costly clinical trials, which would significantly increase the costs associated with bringing a generic drug to market. Some free trade agreements also restrict the ability of a country to issue CLs<sup>10</sup> [119]. Such restrictions can seriously impact a country's access to medicine initiatives, particularly in the area of HIV/AIDS.

Also problematic is a lack of transparency in patent information. This has exacerbated the access problem in LMICs and hampered the ability of countries to procure generics because it creates uncertainty as to what drugs are patented and what are not. An example of the lack of transparency problem can be seen in the case of the avian flu outbreak of 2005. Needing large quantities of generic versions of the drug oseltamivir, many LMICs began considering their options with respect to either voluntary or compulsory licenses. However, some countries were later told by Roche (the patent-holder) that no patents were in force [27].

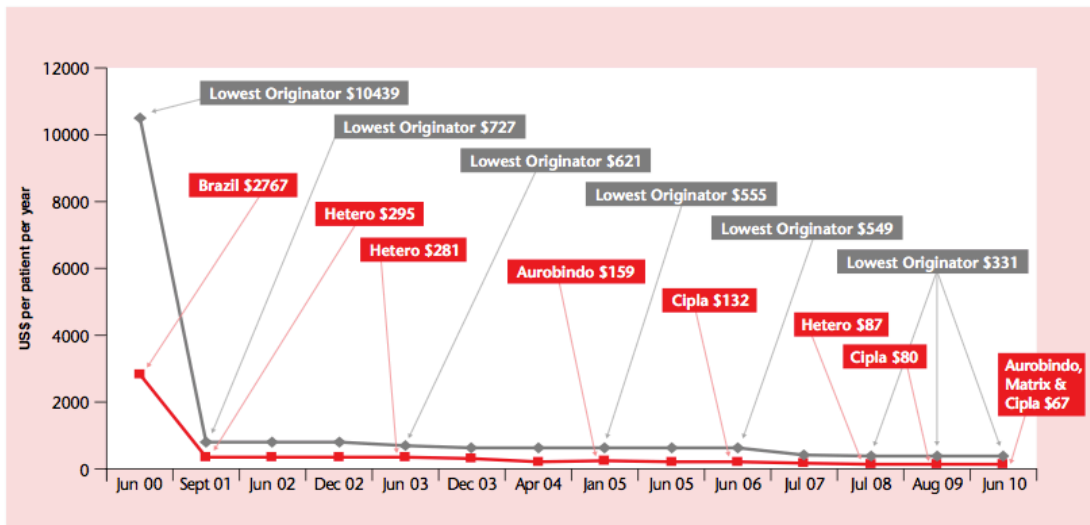
## **2.2 IP Barriers to ARVs**

Despite the plethora of barriers to access to medicines in LMICs, IP barriers remain a significant barrier to accessing ARVs in LMICs. While many older ARVs have become affordable because the patents on them have expired, newer, less toxic ARVs are patented and thus largely unaffordable. Patent protection remains such a significant

---

<sup>10</sup> For example, the US-FTAs with Singapore and Jordan prohibit the issuance of compulsory licenses except for in the event of a "national emergency of other circumstance of extreme urgency" [as opposed to TRIPS, which grants governments broad discretion in determining when to issue a compulsory license]; The US-Morocco FTA similarly limits the issuance of compulsory licenses to circumstances of "extreme urgency" or "national emergency" and to certain diseases (HIV/AIDS, TB, malaria, and other epidemics).

barrier because without generic competition, which serves as a major catalyst for price reductions (Figure 2), the prices of drugs remain so high as to be out of reach for many. Generic market entry is significant because it not only makes lower-cost, bioequivalent drugs available, but also reduces prices of originator drugs.



**Figure 2: Generic Competition as a Catalyst for Price Reductions**

Patents are also a significant barrier to the development of FDCs. In order for a generic company to manufacture a FDC in which more than one component is patented, generic companies must negotiate individual licensing agreements with a number of patent holders, a process that can be costly and time-consuming. Additionally, patent holders can simply refuse to license their patents, barring production of an FDC even if

the other components are available<sup>11</sup> [2, 120]. As a result, certain key first- and second-line FDCs either don't exist or are not available in sufficient quantities in LMICs<sup>12</sup> [2].

While a number of ARVs are available in LMICs, the treatment of HIV/AIDS in LMICs requires pediatric and heat-stabilized formulations, which are not required in developed nations. For these formulations, there is no market-driven solution for their production. Like NDs, pediatric and heat-stabilized formulations are a need exclusive to the developing world, and thus there is little incentive for pharmaceutical companies to engage in R&D and innovate in this area.

The pediatric ARV market is quite small, representing less than 7% of all people living with HIV who are treated. Because of this small market size, pediatric HIV is really a ND, and there is a significant market failure with respect to pediatric formulations. Because so few children are born with HIV in developed nations, there is not a lucrative market for pediatric ARVs, and thus there is little incentive for pharmaceutical companies to develop pediatric formulations. The small pediatric ARV market is further fragmented into smaller niche markets because pediatric HIV treatment changes as children move through different stages of development. This

---

<sup>11</sup> The key second-line FDC, ATV/r, was not available in a generic form until the patent over ritonavir (r) was successfully opposed in India in 2011. Prior to this patent opposition, ATV was being produced in generic form in India, where the patent on ATV was previously rejected.

<sup>12</sup> For example, only 1 Indian generic manufacturer currently sources the entire global supply of generic ATV/r for adult use because of patent protection over ritonavir in other LMICs.

requires not just the development of one pediatric formulation, but the development of multiple products in varying doses and delivery formats as children move from infancy to adulthood [121]. The result of this is that there is currently only one triple FDC that is suitable for children, and one-third of ARVs are currently unavailable in pediatric formulations [28]. The fact that there are any ARVs available for children is quite remarkable, and it likely due to purchase commitments from organizations like the Clinton HIV/AIDS Initiative, which has stimulated the development of pediatric formulations by ensuring a market for pharmaceutical companies [28].

### **2.2.1 India's Role in Access to ARVs in LMICs**

India has been instrumental in supplying low-cost drugs to the developing world, often being referred to as “the pharmacy of the developing world.” Indian manufacturers produce more than 80% of annual purchase volumes of ARVs that go to LMICs, including 88% of all FDCs and 91% of all pediatric formulations [29].

India positioned itself to play this role by taking full advantage of TRIPS flexibilities, refusing to recognize patents for pharmaceuticals<sup>13</sup> until 2005 when such patent protection was mandated by TRIPS. This move by the Indian government allowed India to develop a robust generic drug industry, as there were no patent

---

<sup>13</sup> Prior to the 2005 amendments to the Indian Patent Act, India granted only process patents on pharmaceuticals, so that many inventors could patent the same final drug product, provided that it was formulated through a novel process.



barriers to manufacturing cheap drugs for the developing world. Since the inception of the generic drug industry in India, the business models of Indian firms have been focused on the production of high-volume, low-margin products like generic ARVs.

Since the implementation of TRIPS in 2005, the landscape for access to affordable drugs has changed. Although most first-line ARVs are off-patent, newer second- and third-line treatments that are more effective, have fewer side effects, and lead to less drug resistance have been patented<sup>14</sup> [122], preventing Indian generic companies from producing the drugs for LMICs. Drugs like etavirine, raltegravir, and maraviroc, which are needed for treatment for people who have failed on first-line treatments, lack available generic treatments because they are now patented in India [30]. This has somewhat curtailed India's ability to supply cheap drugs to LMICs because generic manufacturers are unable to enter the market and create the kind of competition that leads to the dramatic price reductions seen in the past with first-line ARVs [4].

However, despite being obligated to grant patent protection, India has maintained its public health commitment by granting compulsory licenses when

---

<sup>14</sup> India has granted patents on the following ARVs: ABC for pediatric use (patent held by GSK); EVG (patent held by Gilead); ETV (patent held by Janssen); FPV (patent held by GSK); MVC (patent held by Pfizer); an improved composition of SQV (patent held by Roche); TAF (patent held by Gilead). The following ARVs have pending patents in India: ATV (filed by BMS); COBI (filed by Gilead); DTG (filed by GSK); a liquid composition of 3TC (filed by GSK); an extended release formulation of NVP (filed by Boehringer Ingelheim).

necessary<sup>15</sup> and maintaining a high threshold for patentability—reserving patent protection for original drugs only and refusing patent protection for minor improvements to existing drugs or reformulations of known chemical compounds.<sup>16</sup> As a result of this high patentability threshold, patents on a number of important ARVs—TDF, darunavir, LPV/r, and atazanavir—have been rejected [12]. This has allowed Indian generic companies to continue to supply affordable ARVs to LMICs.

India’s role as the “pharmacy of the developing world” is changing. Free trade agreement negotiations may further jeopardize India’s ability to supply low-cost drugs to LMICs.<sup>17</sup> However, India will continue to play an instrumental role in supplying drugs to LMICs because it is one of the only countries in the developing world with significant manufacturing capabilities.

### **2.3 Barriers to ND Research**

The ND drug landscape represents a classic case of market failure for which the conventional patent-based drug discovery system is ill equipped to solve. Because R&D is market-driven and pharmaceutical companies seek the highest return on their R&D

---

<sup>15</sup> For example, in 2012 India issued a compulsory license authorizing Natco Pharmaceuticals to make and sell generic versions to the cancer drug Nexavar.

<sup>16</sup> In a recent challenge by Novartis to India’s patent laws, the Indian Supreme Court upheld India’s patentability standards and denied patent protection for a Leukemia drug that was only a minor improvement over the original patent. India also revoked a Roche patent for the antiviral drug Pegasys.

<sup>17</sup> For example, the India-EU FTA encourages patent “evergreening.” Patent evergreening allows pharmaceutical companies to extend their market exclusivity for a drug by making minor changes to a drug whose patent is about to expire in order to gain an entirely new patent over the drug.

investments, the R&D system is heavily focused on developing new drugs for diseases that primarily affect developed nations (e.g. arthritis, diabetes, depression, obesity and acne) [31] or on discovering minor therapeutic changes to currently successful drugs that can then be re-patented. For global diseases—diseases endemic to LMICs but for which a therapeutic market still exists in developed countries—drug innovation occurs because there is sufficient market demand for pharmaceuticals [32]. However, in the case of NDs, innovation rarely occurs because of the timely and costly process of drug development, which requires not only the discovery of a novel drug that may be effective against a target disease, but the demonstration of a drug’s efficacy through clinical trials and the eventual manufacture and distribution of the final product [33]. The IP system thus incentivizes R&D only for diseases that capture a profitable market and is ineffective at adequately addressing the health needs of developing countries.

While some NDs are global and capture some marketable profit (e.g. HIV/AIDS and malaria)<sup>18</sup> [34], most NDs (particularly NTDs) have been nearly eradicated in developed countries, and thus lack market incentives necessary to drive R&D for these diseases.<sup>19</sup> Because of the significant technological barriers associated with ND drug

---

<sup>18</sup> These are classified as “Type II” diseases, meaning that they occur in both wealthy and poor nations, and thus R&D incentives exist, but the level of R&D spending is still very low compared to the global disease burden.

<sup>19</sup> These are classified as “Type III” diseases, meaning they occur almost exclusively in poor countries, and thus R&D for them is almost entirely lacking.

development, as well as the small, uncertain product markets that command drugs for NDs, there are few existing financing or policy mechanisms in place to compensate for the risks associated with ND drug development [35].

The lack of market incentive results from the fact that the primary, and sometimes only, consumer base for ND drugs are those living in poverty in LMICs<sup>20</sup> [123, 124], and thus are unable to afford the high prices charged for branded drugs. This has resulted in a situation where only 10% of R&D funding goes towards research on neglected diseases, which affect 90% of the world's population, a phenomenon that has come to be known as the 90-10 gap [36].

In addition to inadequate incentives to stimulate ND R&D, strong IP rights often act as a barrier to innovation in the form of "patent thickets," which limit the ability of researchers wishing to engage in ND R&D from developing new treatments and technologies [37]. These thickets often create complete gridlock with respect to R&D, particularly in the early states of R&D. In addition to cost and time associated with licensing IP rights, even the initial search for who owns rights over certain molecules

---

<sup>20</sup> According to the World Health Organization, NTDs is particular primarily affect "low-income and politically marginalized people living in rural and urban areas." NDs primarily affect those living in poverty in LMICs because the presence of unsafe drinking water, poor sanitation, substandard housing conditions, and little or no access to healthcare increases the incidence of NDs in a given population.

and processes can be overly burdensome,<sup>21</sup> and thus it is not surprising that ND R&D remains stymied [38].

For NDs for which treatments are available, pharmaceutical companies holding patents often charge prices that are unaffordable, making treatment inaccessible to the world's poorest<sup>22</sup> [125]. Additionally, with respect to NDs for which treatments are available, in many cases the treatments are very outdated and are becoming less effective due to a high incidence of drug resistance [34]. The greatest example of this can be seen with TB. In addition to a vaccine, which is not effective in adults and only partially effective in infants, that has not been updated since 1924 and a first-line drug regimen developed in the 1960s, [39] half a million patients *every year* develop multi-drug resistant TB, for which adequate treatment is not available [37].

### **2.3.1 The Potential Role for India and other Emerging Economies in ND R&D**

Emerging economies have recently been playing a role in ND R&D. Within the past few years, an Indian generic firm has developed a drug for the treatment of visceral leishmaniasis and a Brazilian manufacturer has developed a treatment for skin infections in patients with leprosy [40]. In addition to drug development, Brazil has

---

<sup>21</sup> For example, when the University of Iowa wanted to study a rare ocular disease, it had to contact 71 different entities just to determine ownership of IP rights.

<sup>22</sup> For example, the cost of the best (most effective) treatment for the ND visceral leishmaniasis (VL) is \$454 per patient. The actual cost of the medication is \$150, but treatment is administered intravenously over the course of 20 days, requiring patients to pay additional costs for hospital stays.

invested \$10 million in seventy-six different projects as part of a pilot R&D program, with ultimate aims of finding treatments for TB, malaria, Chagas disease, leprosy, and leishmaniasis [40].

Countries like China, India, Brazil, and South Africa, which have developed generic pharmaceutical industries, have an interest in engaging in ND R&D because, unlike multinational pharmaceutical companies based in developed countries, their populations are affected by NDs. They are also in a better position to engage in ND R&D because, although the market for ND drugs is small, the costs of R&D in these countries is much lower than R&D costs in developed countries<sup>23</sup> [40]. This can be attributed to a number of factors, particularly “lower fixed asset costs (i.e., lower costs of building manufacturing facilities), cheaper labor, lower costs of regulation, efficient manufacturing processes, a large suitable population to be recruited quickly and cheaply for clinical trials, and inexpensive marketing” [40].

---

<sup>23</sup> R&D and manufacturing costs in India and China are one-eighth and one-fifth, respectively, of the costs incurred by Western pharmaceutical companies.

## **3. Overview of Mechanisms to Facilitate Broader Access to Medicines**

### ***3.1 Facilitating Access to ARVs***

The first step in facilitating access to ARVs in LMICs is delaying implementing patent protection until required by TRIPS or, if patent laws are in place, restricting patentability criteria. However, once a patent is granted, the ways in which broader access is facilitated must focus on making ARVs more affordable, and since the beginning of the AIDS crisis, a number of difference mechanisms have been used to increase access to ARVs.

One method that has been used to reduce prices is licensing, either voluntary or compulsory. A number of pharmaceutical companies have also agreed to not assert their patent rights over ARVs in a number of developing countries (known as “non-assert declarations”). Pharmaceutical companies have also offered “tiered pricing” arrangements to certain developing countries, selling patented drugs at a much lower cost than they are sold for outside these countries or, in some cases, donating drugs to LMICs.

However, these initiatives alone fall short for a number of reasons. Most arrangements exclude a number of MICs with high HIV burdens, making facilitating access more difficult in these countries. These approaches are also on a drug-by-drug

and country-by-country basis, so they fail to address the problem globally. Most, with the exception of compulsory licensing, also depend on the on-going goodwill of pharmaceutical companies.

Because the WHO now recommends newer, less toxic first- and second-line treatments for HIV, and because key countries in the scale-up of treatment like India now grant patent protection over newer ARVs, drug prices remain unaffordable for many living with HIV/AIDS in LMICs. Unfortunately, the existing mechanisms to facilitate broader access to these newer, patented drugs fall short, mandating a need for new solutions to the access problem for developing countries as a whole.

### ***3.2 Facilitating Access to ND Drugs***

Recently, there has been increasing attention being paid to the ND problem. A number of initiatives have come to life, and product development partnerships (PDPs) and other collaborations have increased R&D for NDs. However, these alone won't solve the problem, as they are often disease and/or product focused, with little collaboration among these initiatives. In order to adequately solve the ND R&D problem, there needs to also be increased access to research results and increased research collaboration.



### **3.3 Overview of Patent Pools for Global Health**

#### **3.3.1 Patent Pools Generally**

Strong IP rights create a “tragedy of the anti-commons,” restricting the use of knowledge by anyone other than the patent holder. The tragedy of the anti-commons is greatest when relevant patents for a particular product or process are held by a number of different entities; this creates a huge barrier to access and innovation because anyone seeking to expand on existing knowledge must obtain rights from each individual patent holder. Patent pools aim to avert this tragedy by making patented products more readily available.

Broadly speaking, a patent pool is an “agreement among two or more patent owners to license a set of their patents to one another or to third parties” [41]. Such pools function by “collecting a series of patents that relate to the use of a particular technology so that they can be efficiently licensed to those making, using, or selling that technology” [42]. Thus, by making patents more readily available to non-patent holders, patent pools facilitate broader availability of new technologies.

The use of patent pools for facilitate access to technology is not a new phenomenon, as they have been utilized in a number of industries for a variety of reasons<sup>1</sup> and have resulted in a number of benefits to patent holders and industries at

---

<sup>1</sup> Patent pools in other industries have been formed for reasons such as: to establish a technological standard across an industry and to facilitate institutionalized exchange of information that is not covered by patents.

large<sup>2</sup> [43]. In addition to facilitating broader access to technologies, patent pools simultaneously reducing the risks associated with using patented technologies and decrease the time and cost associated with individual license deals.

### **3.3.2 Patent Pools for Global Health**

Patent pools for global health represent a novel way to move beyond the status quo in initiatives aimed at increasing access to ARVs and facilitating ND R&D. Like other patent pools, patent pools for global health aim to overcome some of the shortcomings associated with the current market-based IP landscape. By managing IP from a public health perspective, global health patents pools have the potential to “counteract high prices, spur needs-driven research, and facilitate innovation,” [28] making medicines more available and affordable.

While the experiences of other patent pools can be instructive, patent pools for global health are different from other patent pools. Unlike most patent pools, which involve either cross-licensing among competitors in order to share patents necessary for the manufacture of a particular technology or industry-wide patent pools that are necessitated by the need for an industry-wide standard, patent pools for global health

---

Examples of patent pools are: the SARS vaccine patent pool; the Golden Rice patent pool; and the aircraft patent pool.

<sup>2</sup> For example, the sewing machine patent pool led to a substantial reduction in licensing costs as compared to original fees charged; the MAA and auto industry patent pools brought an end to ubiquitous litigation.

involve a distinct set patent donors, who license their technology into the pool for reasons other than profit, and patent users, who use the IP in the pool without also donating into it [12]. This changes the dynamic of the patent pools for global health as compared to other patent pools, as it is necessitated not by practical or monetary concerns, but rather humanitarian concerns, and thus proper incentives need to exist to compel patent holders to donate into the pool.

Two patent pools for global health have recently been formed—the Medicines Patent Pool (MPP) and WIPO Re:Search Consortium. While both are patents pools for global health, they are significantly different in terms of disease focus and inputs. The MPP is a patent pool for ARVs; it aims to overcome the IP barriers that currently bar production of newer ARVs that are more effective and less toxic. The inputs into the pool are patents related to the development and manufacture of patented ARVs, and the pool aims to increase production of generic ARVs and eventually stimulate downstream development of new FDCs that are better suited to the needs of developing countries.<sup>3</sup>

Re:Search is a patent pool for compounds, data, and know-how related to NDs. Unlike the MPP, which focuses on downstream innovation, Re:Search focus is on stimulating upstream innovation of entirely new drugs for NDs. By facilitating the exchange of information and providing users with access to patents, data, and know-

---

<sup>3</sup> One goal of the MPP is to facilitate production pediatric and heat-stabilized formulations that are lacking in developing countries.

how associated with NDs, Re:Search aims to speed up the development of new ND drugs and reduce the financial and administrative burdens associated with licensing arrangements, which may be necessary after product development [44]. The real value in Re:Search is that it facilitates collaborations, overcomes information barriers, and reduces transaction costs, helping those wanting to develop ND drugs and technologies locate and work with the holders of relevant patents, data, and know-how [12]. It also may help overcome the tragedy of the anti-commons with respect to upstream knowledge, products, and processes that are currently under-utilized because multiple parties hold varying rights over necessary inputs for downstream products [45]. In this way it overcomes the patent thicket problem that currently prevents researchers from sharing and using knowledge to develop new medicines, vaccines, diagnostics, and other technologies for NDs.

## **4. Traditional Mechanisms that Facilitate Access to ARVs**

Nearly all originator companies with HIV/AIDS treatments are now engaged in some form of initiative to promote access to ARVs in developing countries, whether through voluntary licenses, non-assert declarations, tiered pricing, or drug donations. Despite these efforts, costs remain high, particularly for newer drugs, and access remains limited. While all of these efforts are certainly a step in the right direction, nothing can substitute for generic competition, which is achieved only through licensing. Ultimately, all of these mechanisms have shortcomings that cannot be overlooked, as they all operate on a drug-by-drug and country-by-country basis and fail to address the access problem globally.

### ***4.1 Voluntary Licensing***

Under voluntary licenses, pharmaceutical companies holding patents on HIV drugs authorize a generic manufacturer to manufacture and sell the drug. Due to a lack of transparency, the terms of voluntary license agreements are not readily available, but the agreements generally set out a number of requirements relating to the geographic scope of the license, the payment of royalties, formulations of combination products, sourcing of active pharmaceutical ingredients (APIs), technology transfer, data exclusivity, and provisions relating to compulsory licenses [46].

A number of originator companies have signed voluntary licenses with generic manufacturers, and at least seven originator companies<sup>1</sup> with HIV drugs in their patent portfolio engage in voluntary licensing as part of their stated access to medicines policies [46]. There is little public information available about the terms of individual license agreements, but the information that is available suggests that the terms vary significantly across licenses (Appendix A). Some licenses are better than others, but they all contain one or more restrictions that are quite problematic. However, because licensees often have little negotiating power with respect to the patent holders, they often, and will likely continue to, accept terms that are not ideal.

Though many licenses are royalty-free, some require royalty payments as high as 15% [46]. With respect to APIs, which represent a significant portion of the final price of a drug,<sup>2</sup> some licenses do not allow licensees to manufacture APIs,<sup>3</sup> while others give licensees the freedom to manufacture and sell APIs [46].

With respect to FDCs, some licenses permit only those combinations specified in the license,<sup>4</sup> some require pre-approval from patent holders before any combination

---

<sup>1</sup> Abbott, Boehringer-Ingelheim, BMS, Gilead, J&J, Merck, Roche, and ViiV all include voluntary licensing in their access initiatives.

<sup>2</sup> For some drugs, APIs can represent as much as 40-50% of the cost of goods sold.

<sup>3</sup> For example, the Johnson & Johnson licenses for ATV and DRV .

<sup>4</sup> Johnson & Johnson license for RIL permits combinations only with TDF/FTC.

products are made,<sup>5</sup> and some grant licensees the freedom to co-formulate with any other products.<sup>6</sup> Illustrative of the impact of FDC formulation restrictions is the case of a new WHO-recommended first-line FDC that consists of tenofovir (Gilead), lamivudine (GSK) and either nevirapine (Boehringer-Ingelheim) or efavirenz (Bristol Myers Squibb). A FDC of these drugs currently does not exist or is in limited supply [28], largely because any manufacturer wishing to develop it would have to not only seek voluntary licenses from all three or four patent-holders, but would also have to negotiate the freedom to make FDCs in the license agreements. FDC restrictions can be particularly significant for drugs that have the potential to be used pediatric or heat-stabilized formulations. Because pharmaceutical companies neglect developing these formulations, barring licensees from developing these formulations might foreclose product development entirely.

With respect to technology transfer, data exclusivity, and the ability of licensees to challenge patents or supply drugs to countries that issue compulsory licenses, information is not publicly available [46]. If voluntary licenses restrict the ability of licensees to supply drugs to countries that have issued a compulsory license, this would dramatically limit the usefulness of compulsory licenses as a tool to facilitate broader access to ARVs.

---

<sup>5</sup> For example, the Gilead-MPP license for EVG.

<sup>6</sup> For example, the Gilead-MPP license for TDF and COBI.

While the geographic scope of voluntary licenses varies significantly, there is a general trend of limiting licenses to supply in LDCs, Sub-Saharan Africa, and India; lower-middle and middle-income countries tend to be excluded entirely. To date, there is not a single voluntary license that covers all low- and middle-income countries [47].

Despite the restrictions contained in most voluntary licenses, they have nevertheless played a significant role in promoting broader access to ARVs, as they have introduced some level of competition into the market and thus made ARVs covered in a license more affordable to those living in LMICs. Because patent protection is not granted in India and other MICs, voluntary licensing is a way to get generics on the market much more quickly than waiting for a patent to expire or waiting for the patent board to rule on a pre-grant opposition of the patent [127]. Voluntary licensing can also operate as an important tool for north-south technology-transfer, allowing generic companies in developing countries that become licensees to gain knowledge and expertise from developed-country drug manufacturers [126]. By allowing for such technology-transfer, voluntary licenses can help speed up the development of the drug manufacturing industry in countries that are in the early stages of developing manufacturing capabilities. Additionally, if voluntary licenses contain data exclusivity waivers, this can further speed up the timeline for when a generic reaches the market, as licensees will not have to conduct their own lengthy, costly clinical trials [127].



However, regardless of the benefits of voluntary licenses, they are ill-equipped to solve the problem of access to ARVs globally because they are all drug-specific and country-specific, and thus don't represent a true global solution. Additionally, because the number of licensees that patent holders will sign agreements with is often limited in number, voluntary licenses do not bring about the level of robust generic competition that, in the past when patents were not an issue, dramatically brought down prices of ARVs, even if they do somewhat bring down prices. Additionally, generics on the market that are not under a voluntary license are usually cheaper than generics offered under a voluntary license<sup>7</sup> [127]. Another problem with relying on voluntary licenses to solve the access problem is that they depend on the on-going goodwill of pharmaceutical companies.

## ***4.2 Compulsory Licensing***

Compulsory licensing is an important tool that can be utilized within the current IP system to promote access to ARVs, and can be really instrumental in bringing down prices of ARVs. In Thailand, for example, a compulsory license issued in 2007 for the drug LPV/r brought prices down in some middle-income countries by 79%, from \$2,200 per patient per year to \$470 [4]. Despite their ability to bring about such significant price

---

<sup>7</sup> For example, in 2006, Lamivudine (offered by generic manufacturer Aspen under a voluntary license from GSK) is priced at \$69 per patient per year, whereas the generic manufacturer Cipla (not under a voluntary license) offers it for \$51 per patient per year and by Aurobindo (also not under a voluntary license) for \$54 per patient per year. Similarly, the drug Nevirapine, under voluntary license, is priced at \$97 per patient per year, whereas the price for generics not under a voluntary license is \$61 per patient per year.

reductions, compulsory licenses have historically and continue to be under-utilized as a means for reducing drug prices. Since the mid-1990s, governments have only proposed compulsory licenses around twenty-five times, with very few occurring since 2008 [48].

The problem with relying on compulsory licenses is that the granting of them relies on the political will of developing-country governments to address the health needs of their populations. Additionally, countries that grant compulsory licenses often face direct or indirect retaliatory measures for pharmaceutical companies and governments of other countries. For example, Thailand's granting of compulsory licenses resulted in the pharmaceutical company Abbott refusing to supply Thailand with any of their new ARVs and the imposition of trade sanctions by the United States<sup>8</sup> [128]. In Indonesia, a presidential decree in authorizing compulsory licenses for ARVs resulted in PHRMA claiming that it had abused compulsory licensing rules and could "reduce the incentive to invest in future R&D."

Even the threat of a compulsory license can impact prices of ARVs, because it can serve as an impetus for voluntary price reductions. In one analysis of compulsory licenses, over half of the instances in which LMIC governments initiated the compulsory licensing process ended with the patent holder issuing a voluntary license, giving a discount on the drug, or even giving the branded drugs away [48]. Brazil has threatened

---

<sup>8</sup> This included being placed on the United States Special 301 watch list and the withdrawal of three export products from US GSP [generalized system of preferences] status, which resulted in tariffs of 3.9%-6.5% being imposed on the three products.

compulsory licenses a number of times since 2001, and in every instance it has led to drug discounts or voluntary licenses [23]. In 2006, Gilead established a voluntary license allowing for the distribution of a low-cost generic version of tenofovir in a number of countries. However, China was excluded from this deal, and has recently threatened to issue a compulsory license; Gilead is now reportedly negotiating a deal with the Chinese government in which they will donate a substantial amount of tenofovir to China [48]. However, smaller countries are at a serious disadvantage because they do not have the same level of negotiating power that larger countries have, and thus they are less likely to get the sorts of deals that countries like Brazil and China are able to obtain.

Compulsory licenses, whether enacted or threatened, are a powerful tool for LMICs to stimulate price reductions on ARVs. However, because “health ministries are generally more interested in receiving price reductions for specific drugs than in dramatically overhauling the patent system”[48], compulsory licensing does not change the status quo with respect to drug prices, because countries take the price discounts rather than issuing a compulsory license and allowing for generic market entry. Additionally, because compulsory licenses must be granted on a country-by-country basis, at a global level this approach to increasing access to ARVs is “less likely to achieve economies of scale rapidly, would entail higher transaction costs, imply greater uncertainty for generic producers, and require significant political capital” [28].

The circumstances surrounding the granting of a compulsory license, as well as its benefits and drawbacks are best exemplified by the case of the compulsory licensing issued in Thailand.

#### **4.2.1 Compulsory Licenses in Thailand**

Thailand's AIDS epidemic was the first major Southeast Asian epidemic, and by the early 1990s it was considered to be the fastest growing AIDS epidemic in the world [49]. For over a decade, the Thai government was unable to procure affordable ARVs for its citizens. Thailand remained heavily dependent on foreign aid for the funding of ARVs, resulting in the majority of the population being unable to obtain treatment. Costs for ARVs remained so high that when Thailand adopted a universal health care scheme, ARV treatment was initially excluded [50].

This changed in 2001, when the Thai Government Pharmaceutical Organization (GPO) developed drug-manufacturing capabilities and began production of a generic, fixed-dose combination ARV called GPO-VIR<sup>9</sup> [51]. The domestic production of GPO-VIR was crucial to increasing access to treatment, as it resulted in an eighteen-fold decrease in the cost of treatment [52]. This cost reduction expanded treatment coverage significantly—by the end of 2006 the number of patients receiving treatment increased from under 5,000 in 2002 to over 80,000 [51] and over 80% of people living with AIDS had access to public ARVs, an increase from almost 0% [53]. Due to drastic price

---

<sup>9</sup> A first-line triple FDC containing stavudine (d4T), lamivudine (3TC), and nevirapine (NVP)

reductions associated with domestic production of ARVs by the GPO, Thailand was able to adopt a policy on universal access to ARVs under its universal health care scheme [54]. Without the prevention and treatment efforts implemented by the Thai government after generic production of ARVs began, it is estimated that the HIV/AIDS disease burden in Thailand would be fourteen times more than what was actually experienced [53].

Despite Thailand's success in addressing the HIV/AIDS epidemic, adverse side effects and high levels of drug resistance to GPO-VIR prompted the need to look towards procuring newer drugs with fewer side effects and less resistance [52]. Unfortunately, this came at a time when Thailand was fully TRIPS compliant, and thus unable to produce or import the drugs necessary to meet the needs of their infected population. In 2006, Thailand addressed these needs and issued a compulsory license for the ARV Efavirenz [55]. This license allowed the Thai GPO to import or produce generic versions of Efavirenz, resulting in the number of people having access to a steady supply of the drug to increase from around 4,500 before the license to over 29,000 people by the end of 2010 [56]. In 2007, following failed negotiations to lower prices on a newer, second-line ARV, Thailand issued another compulsory license for the production or importation of LPV/r [55]. After the Thai GPO began importing a generic version from India, the cost of treatment was drastically reduced from \$2,200 per patient per year to \$600 per patient per year [57]. This increased the number of people having

access to a steady supply of the drug from almost none to over 6,000 by the end of 2010 [57].

Unfortunately, the issuance of compulsory licenses in Thailand was not without its drawbacks, as Thailand faced retaliatory measures from pharmaceutical companies and the United States government. In 2007 Abbott, the patent-holder on LPV/r, was so angered by Thailand's decision to grant a compulsory license that they withdrew all of their pending patent applications and refused to supply any of their newest drugs there, one of which was a new, heat-resistant formulation of LPV/r [58]. In 2006, Thailand was placed on Office of the United States Trade Representative's (USTR) "Special 301" Report Watch List, based on a concern surrounding weak patent protection over pharmaceuticals [59]. In 2007, Thailand was elevated to the "Special 301" Report *Priority* Watch List; in the same year the USTR also removed GPS status for three Thai imports, withdrawing duty-free access to the U.S. market for these products [50]. However, despite these drawbacks, Thailand is one of the few developing countries that has achieved universal access to ARVs [129], and this is primarily attributable to its issuance of compulsory licenses that has helped the government secure a continuous, reliable, affordable supply of ARVs.

### **4.3 Non-Assert Declarations**

Non-assert declarations<sup>10</sup> are part of the stated access initiatives of a number of pharmaceutical companies holding ARV patents. With these declarations, patent holders make a commitment that they will not enforce patents in certain countries, under certain circumstances [60]. With these declarations in force, third parties are permitted to manufacture and sell or import the patented ARV within a specified scope without fear that the patent holder will bring an infringement suit [60].

These declarations are becoming increasingly popular with pharmaceutical companies. Novartis, Roche and Lilly do not file new patents or enforce old patents in LDCs [60]. Boehringer Ingelheim has granted non-assert declarations to WHO pre-qualified generic manufacturers to manufacture and sell the ARV tipranavir and products containing nevirapine [60]. Janssen Pharmaceuticals has granted a non-assert on the second-line ARV darunavir [60].

Non-assert declarations, in theory, have the potential to increase access to low-cost generics in LMICs, but unfortunately are often geographically restricted. The Boehringer Ingelheim non-assert allow for sale of drugs only to seventy-eight countries—low-income countries, all LDCs<sup>11</sup> and all African countries [60]. Similarly, the

---

<sup>10</sup> Also referred to as “non-assert covenants” and “immunity from suit agreements.”

<sup>11</sup> Low-income countries are those countries classified by the World Bank as having a GNI per capita of \$745 or less. LDCs are a subset of low-income countries that suffer from the most severe structural impediments to sustainable development.

Lilly, Roche, and Novartis non-asserts apply only to LDCs, and the Janssen non-assert applies only to Sub-Saharan Africa and LDCs.

The problem with non-asserts, particularly for newer, second- and third-line ARVs, is that they exclude middle-income countries. Exemplary of the shortcomings of non-assert declarations is the Johnson & Johnson non-assert with respect to darunavir. The greatest demand for second- and third-line ARVs like darunavir is in middle-income countries, where patients have been receiving treatment for long enough to have developed resistance to first-line ARVs [61]. Because middle-income countries are excluded from the non-assert, patients in these countries have to rely on the goodwill of Johnson & Johnson to offer them affordable prices or to engage in voluntary licensing. Johnson & Johnson has entered into voluntary licenses covering darunavir with two generic manufacturers, but the terms of the license exclude most middle-income countries. Because Johnson & Johnson has not offered sufficiently discounted prices to middle-income countries, prices in excluded countries remain unaffordable, remaining as high as \$6,000 per patient per year in some MICs [61].<sup>12</sup> Because darunavir must be boosted with ritonavir [2], this price represents just one component of treatment. Additionally, because the greatest demand for darunavir is in middle-income countries [61], exclusion of these countries from the non-assert declaration shrinks the global

---

<sup>12</sup> In Brazil, the cost of darunavir is \$6,037 per patient per year; in Georgia, the price is \$8,468 per patient per year; in Thailand, the price is \$4,854 per patient per year.



market for darunavir. This creates a situation where generic manufacturers currently do not have adequate incentives to produce generic darunavir, because they are unable to sell to the largest market base for the drug. Also problematic is Johnson & Johnson's declaration that it would "assert its patent rights if – in its unilateral judgment – darunavir was being produced in sub-optimal formulations or dosages" [61]. While quality assurance is vital for effective antiretroviral treatment, Johnson & Johnson has failed to comment on how they will make this "unilateral judgment," creating a lot of uncertainty around the production of darunavir. Additionally, Johnson & Johnson has not clarified whether or not they will allow co-formulation with darunavir under the non-assert. This is problematic because darunavir requires co-formulation for its effectiveness, requiring boosting with a protease booster [2]. All of the uncertainty surrounding the darunavir non-assert underscores why generic manufacturers are hesitant to produce generic formulations of drugs operating under non-assert declarations.

In theory, non-assert declarations could lead to the generic manufacture of ARVs. However, they are not a real, long-term solution to the access problem because they depend on the on-going goodwill of pharmaceutical companies. There is also a lot of uncertainty surrounding non-assert declarations with respect to how long generic manufacturers will have the freedom to produce a generic. Because generic manufacturers would have to stop production in the event that a pharmaceutical

company decides to assert its patent rights, there is little incentive to invest in drug development.

#### **4.4 Drug Donations**

A number of organizations<sup>13</sup> pour billions of dollars each year into increasing access to ARVs. In 2008 alone, \$15.6 billion was spent on AIDS programs in LMICs, with a substantial portion of that going to ARV procurement [12]. These programs have been instrumental in the scale-up of HIV treatments in LMICs, but the focus tends to be pretty narrow, with most of the money being funneled into HIV/AIDS, TB, and malaria.

While assistance in the form of drug donations undoubtedly increases the number of people who have access to ARVs, such assistance is unsustainable, particularly as governments and organizations face increasing financial constraints. While international assistance for HIV/AIDS programs in LMICs have risen dramatically since the early 2000s, donor funding began to flat-line in 2008 at the onset of the global economic crisis, and in 2011, began to decline [130]. This is significant because as the demand for newer, more expensive ARVs increases and donor budgets shrink, the need for access to affordable ARVs becomes increasingly pressing. However, because these newer ARVs are patented in India and other MICs, generics are not available. Thus, organizations have to either pay the branded price or negotiate individually with drug companies for lower-cost branded drugs. Like non-asserts, this depends heavily on the

---

<sup>13</sup> Notably, GAVI, the Global Fund, The Bill & Melinda Gates Foundation, PEPFAR, and CHAI.

continuing good will of pharmaceutical companies to offer organizations prices that are low enough such that they can afford to continue donating ARVs to LMICs.

In some instances pharmaceutical companies will donate drugs to countries or donor organizations.<sup>14</sup> While drug donations can be hugely beneficial in cases on national emergencies or other instances where drugs are not available in sufficient quantity globally because of a lack of a sustainable market, as in the case of NDs<sup>15</sup> [131]. However, for a chronic disease like HIV that requires a lifetime of treatment, drug donations are not sustainable. In addition to drug donations for HIV being unsustainable, they can negatively impact generic competition, as these organizations are financially constrained and will accept donations rather than purchase drugs from generic manufacturers.

Thus, drug donations do not encourage long-term solutions to the access problem, particularly the generic manufacture of ARVs. Because “health ministries are generally more interested in receiving price reductions for specific drugs than in dramatically overhauling the patent system” [48], they are willing to accept drug donations rather than make a commitment to a more long-term solution. Drug

---

<sup>14</sup> For example: Pfizer has donated Diflucan; Merck has donated Mectizan; Boehringer has donated Viramune.

<sup>15</sup> For example, the Merck donation of Mectizan for treatment of river blindness has been very successful, providing treatment to millions living in LMICs. However, this donation’s success can be largely attributed to the fact that river blindness is geographically isolated to a few regions, has a very simple treatment protocol, and has the potential to be eradicated. Drug donations in the context of HIV are much more complex, as HIV requires a lifetime of constantly evolving treatment.

donations thus fail to change or challenge the existing IP regime or allow LMICs to become self-sustainable. Without promoting generic competition, long-term drug prices will likely remain high. By decreasing the market for donated ARVs, drug donations deter generic market entry because they increase the risk associated with investing the time and costs to produce a generic ARV [133]. Thus, even if ARVs are available for free today, if drug donations stop, prices will potentially remain high if the donations are on a large enough scale that they deter generic market entry.

Additionally, pharmaceutical company donations of ARVs are often limited in time, scope, and geography. For example, Boehringer-Ingelheim announced a drug donation program for nevirapine in 2000, but the donation was only for the prevention of mother-to-child transmission of HIV, without any provision for follow-up treatment, and was only available for fifty-nine low-income countries [132].

Like non-asserts, drug donations are an unsustainable method of increasing access to ARVs in the long-term because their success depends on the ongoing good will of pharmaceutical companies. While the threat of a compulsory license has, in the past, prompted pharmaceutical companies to donate drugs in some circumstances, this has only really been seen in countries like South Africa and Brazil that have large enough economics to give them negotiating power.

## **4.5 Tiered/Differential Pricing**

Almost all pharmaceutical companies with ARV patents engage in some form of tiered or differential pricing, whereby they sell drugs at different prices in developed and developing countries, as well as different prices in low-income and middle-income countries. Although the price discounts on ARVs are lower than they would be without tiered-pricing arrangements, drug prices are often still high compared to the prices of generics [62], particularly in those countries excluded from a pharmaceutical company's lowest pricing tier [2].<sup>16</sup>

The biggest problem with differential pricing is that middle-income countries, with the exception of India and South Africa, are almost always excluded from tiered-pricing arrangements. While India and South Africa have been able to obtain inclusion in tiered pricing arrangements, this is possibly due to international pressure, in the case of South Africa, and a high level of bargaining power due to high manufacturing capabilities, in the case of India. This is problematic because, in addition to LMICs being

---

<sup>16</sup> There are some exceptions to this, with discounted prices by patent holders being cheaper than generic equivalents. One case is darunavir, which is offered by Johnson & Johnson for \$810 per patient per year for the lowest-tiered pricing country category and the generic company Aspen for \$861 per patient per year. Similarly, the Johnson & Johnson price for Etravirine is \$438 per patient per year for the lowest tiered pricing country category and the generic price offered by Aspen is \$467 per patient per year, and the lowest price offered by Johnson & Johnson for LPV/r ranges from \$108 per patient per year to \$265 per patient per year for different formulations, whereas the generic price ranges from \$150 per patient per year to \$389 per patient per year from a number of manufacturers. However, Johnson & Johnson have voluntary licenses in place for these drugs, which may explain the price difference. The only real outlier is Ritonavir, which is offered by AbbVie for \$83 per patient per year and by Mylan for \$178 per patient per year and by Cipla for \$316 per patient per year. It is unclear what explains this price difference.

financially differentiated from developed countries, many middle-income countries are high differentiated nationally. Because of the high levels of income inequality that are pervasive in almost all middle-income countries<sup>17</sup>, close to 70% of the world's poor [63], and most of the world's poorest billion [8], reside in middle-income countries. Despite these levels of poverty, middle-income countries are almost always excluded from tiered-pricing arrangements because there are enough people in these countries with incomes high enough such that they are able to afford higher-priced drugs [64]. While some pharmaceutical companies, like Gilead, have included a number of middle-income countries in their tiered pricing arrangements, Abbott, Merck, Johnson & Johnson, and ViiV Healthcare all excluded all middle-income countries entirely from their tiered pricing categories, even if drugs are being purchased from donor organizations like PEPFAR and the Global Fund, resulting in drug prices in middle-income countries being negotiated on a per-country basis [63].

These negotiations have the potential to lead to significant price discounts, but smaller middle-income countries that lack significant negotiating power often pay much higher prices than larger countries. For example, in 2006, the price of the ARV LPV/r in Honduras was six times higher than the price in Brazil, despite the fact that both countries have equivalent HIV prevalence rates and Honduras' per capita GNI is one-fourth that of Brazil's [62]. For the second-line drug ATV, Bristol-Myers Squibb

---

<sup>17</sup> For example, South Africa and Brazil are ranked the 8th and 10th most unequal countries in the world.

excludes Southern African countries from its lowest pricing tier. Thus, despite the fact that Southern Africa has the highest HIV prevalence rate in the world, the price of ATV is \$547 per patient per year, 25% higher than the \$412 per patient per year price for the countries in the lowest tier [62].

Despite the shortcoming of these per-country negotiations, particularly for smaller countries, these negotiations can be heavily impacted after the issuance of a compulsory license. Until 2007, middle-income countries had to negotiate on a per-country basis with Abbott for LPV/r. Prices remained high—5,000 in China; \$7,775 in Honduras [62]—until Thailand issued a compulsory license. After the compulsory license, Abbott reduced the price of LPV/r to \$1,000 for fifty-five middle-income countries [62].

Another problem with tiered pricing is that, despite the short-term benefits with respect to price, it does not result in the long-term price reductions that arise through generic competition. This is particularly true for third-line ARVs that are patented almost everywhere. MSF estimates that, with respect to the one potential third-line regimen, tiered pricing will result in costs of \$2,766 per patient per year for the lowest tier, and up to \$6,000 per patient per year for middle-income countries [30].

There are also no international standards with respect to tiered pricing—every pharmaceutical company seems to have different standards for the countries eligible for the discounted drugs [62]. Additionally, like the other alternatives, differential pricing is

not sustainable, as it requires the on-going goodwill of pharmaceutical companies to offer these lower prices.



## **5. The Medicines Patent Pool: A Novel Approach for Increasing Access to ARVs**

### ***5.1 History and Overview of the MPP***

The MPP represents a novel solution to overcoming some of the problems associated with access to ARVs in LMICs. By collectively managing IP rights associated with ARVs, the MPP offers a more global, systematic approach to solving the access problem than what is currently offered by drug-by-drug, country-by-country approaches.

The idea for a patent pool for ARVs was first proposed by Jamie Love in 2002 at the International AIDS Conference. Love's idea was for a patent pool for ARVs based on compulsory licensing, modeled after the US pool for essential airline patents in 1917<sup>1</sup> [65]. Knowledge Ecology International and MSF to UNITAID again proposed the idea in 2006. The initial proposal suggested a focus on the patents required for the development and production of a generic version FDC TDF/3TC/EFV or NPV, for both adult and pediatric use, as well as the development of a generic version of the heat-stabilized drug LPV/r. While some people engaged in access initiatives felt that the

---

<sup>1</sup> Until 1917, it was impossible to manufacture aircrafts without the consent of the patent holders—the Wright brothers and Glenn Curtiss. When World War I broke out, patents related to aircrafts became important for national security. A commission was created to study the problem, with the ultimate result that the Secretary of War and the Secretary of the Navy were able to “secure, by purchase, condemnation, donation or otherwise, such basic patent or patents as they may consider necessary to the manufacture and development of aircraft in the United States for governmental or civil purposes.” This prompted the creation of the Manufacturers Aircraft Association, which formally formed a patent pool for aircraft patents on July 24, 1917.

contributions to the MPP should be compulsory [65], UNITAID rejected this for a variety of legal, practical, and political reasons [42]. The final UNITAID proposal outlined a patent pools based on voluntary contributions from patent holders, with the option for using compulsory licenses to obtain IP rights should a voluntary scheme fail [42]. In 2008, after conducting a legal review of the proposed MPP, UNITAID approved the creation of the MPP and established a task force to design the structure of the pool. In July 2010, the MPP became operational.

The MPP represents a one-stop shop for both patent holders willing to contribute their IP into the pool and generic companies seeking to develop generic formulations of patented ARVs [66]. Patent holders—pharmaceutical companies, researchers, governments, and universities—voluntarily offer sought-after IP related to ARVs to the pool, and any company seeking to use the IP in the pool to produce generics can obtain a license from the pool, after which they can begin the process of developing generics for LMICs. By streamlining the licensing process, the MPP has the potential to drive more rapid formulation of FDCs and foster the development of pediatric drug formulations [66].

The mission of the MPP is to both increase generic competition for ARVs, lowering prices through market-forces, and to bring to developing-country markets generic versions of existing FDCs and new formulations that are better adapted to developing countries [42]. With these aims in mind, three types of products are currently being

licensed in the MPP: (i) products that already have regulatory approval and have generic versions available on the market; (ii) products that already exist as originator products but do not yet have a generic equivalent on the market, so prices remain high; and (iii) entirely new products that are not yet on the market.

Legally speaking, because the MPP relies on voluntary licenses, TRIPS is not relevant to the activities of the pool. However, if, in the future, the MPP were to rely on a compulsory license to obtain access to IP, TRIPS rules related to compulsory licensing for both importing and exporting countries would come into play. A problem with relying on a compulsory license is that national patents laws in some countries may have restrictions with respect to compulsory licensing.<sup>2</sup> Thus, in addition to TRIPS considerations, national patent laws would need to be taken into account.

## ***5.2 Theoretical Benefits of MPP***

The MPP has the potential to offer a number of benefits that go beyond the status quo of current access initiatives. If successful, the MPP has the ability to be instrumental in bringing down the price of ARVs and developing much needed FDCs and pediatric formulations [4]. By providing generic manufacturers with easier, faster access to relevant patents, patients needing treatment will in turn have faster access to better, more affordable treatments.

---

<sup>2</sup> For example, some countries have, in their national patent laws, restrictions on sub-licensing of compulsory licenses.

By facilitating access to multiple patents by multiple manufacturers, the MPP offers the prospect of robust generic competition for drugs in the pool, thereby reducing the cost of ARVs. UNITAID alone spends \$80 million a year on the procurement of ARVs [67]. If the MPP is able to successfully bring down the costs of ARVs, donor organizations would be able to scale-up treatment and/or use the money saved on other initiatives. Scaling-up treatment is not just about getting the cheapest available drugs to patients and increasing the number of people on ARVs; it also requires getting the most effective treatment to patients. While there are cheap versions of some first-line ARVs available, a number of these treatments are toxic and/or pose resistance problems. As more patients need newer, patented ARV for effective treatment, financially constrained donor organizations will not be able to provide these treatments on a large scale unless the drugs are affordable. The MPP has the ability to make these newer drugs affordable by allowing the introduction of generic competition into the market well before the expiration of the patent term.

While there are a number of barriers to the development of new FDCs,<sup>3</sup> patents are arguably the biggest. As a result of these patent barriers, a number of WHO-recommended valid combinations are unavailable in LMICs. By offering sub-licensees technology transfer packages from multiple patent holders, the MPP can foster easier,

---

<sup>3</sup> In addition to patent barriers, producing high-quality and effective FDCs poses a number of technical challenges.

less costly, and more rapid development of new FDCs and formulations [68]. By allowing more than one party to work with patents relevant for a new FDC or pediatric formulation, the MPP has the potential to foster innovation in this area, particularly because pharmaceutical companies do not have incentives to develop formulations for resource-poor settings. The MPP can also simplify the licensing process, thereby reducing transaction costs for combinations [42]. Without the MPP, a generic company would potentially need to obtain licenses from at least three different patent holders in order to develop, manufacture, and sell a FDC. The MPP lowers the coordination and time costs associated with trying to coordinate the right to manufacture and sell FDCs from each individual patent holder [42].

The voluntary nature of the MPP makes its success dependent on the willing participation of patent holders, and thus adequate incentives must exist in order to compel participation in the MPP. In addition to lowering transaction costs for generic manufacturers, the MPP would also lower transaction costs for pharmaceutical companies. Rather than negotiating with a number of different generic manufacturers on a case-by-case basis, patent holders will only have to negotiate one license, with the MPP. Another incentive for patent-holders to join the MPP is the ability to, as donors, use any future patents in the pool that may be granted with respect to new formulations. Joining the MPP may also offer patent holders an alternative to compulsory licensing [69]. If relevant patents are in the pool and readily available in LMICs, there would be

little need for a country to issue a compulsory license to procure a reliable, affordably supply of the drug.

The MPP also offers reputational benefits to patent holders. It is clear now that pharmaceutical companies recognize the need to improve access to ARVs in LMICs, as almost every multinational pharmaceutical company is engaged in one or more access initiative. Joining the MPP can become a part of those access initiatives, and offer reputational benefits by showing that companies are really committed to improving global health.

### **5.3 MPP Engagement**

To date, the MPP has struck seven license deals with five patent holders—the US National Institutes of Health (NIH), Gilead Sciences, ViiV Healthcare, Roche, and Bristol-Myers Squibb (BMS). While all of these licenses have their benefits and shortcomings, they are the only license agreements, voluntary or otherwise, that are publicly available in their entirety, and the MPP’s dedication to transparency with respect to licensing must be commended.

The MPP is currently in negotiations with AbbVie, which holds patents on two of the MPP’s “Level 1” priority compounds<sup>4</sup> (Lopinavir and Ritonavir) and Boehringer-Ingelheim, which holds a patent on the “Level 2” priority compound Nevirapine. Thus

---

<sup>4</sup> The MPP bases priority levels on a medicine’s clinical importance and the existence of market and/or patent barriers that prevent access.

far, Merck and Tibotec/Johnson & Johnson, both of which hold patents on a number of “Level 2” priority compounds, have refused in engage with the MPP.

## **6. Overview of Current MPP Licenses**

### **6.1 NIH License**

In September 2010, the US National Institutes of Health became the first to contribute to the MPP. The MPP-NIH license was a royalty-free, non-exclusive license for LMICs for patents related to darunavir, a protease inhibitors used to treat HIV, particularly drug-resistant HIV. While the license permits sub-licensees to make and use darunavir for research purposes, it is rather limited. Because of others patents, at the time held by Tibotec,<sup>1</sup> related to the manufacture of darunavir, sub-licensees were not permitted to manufacture or sell the drug. Thus, the real benefit of the license was not in its terms but rather what it represented politically—a display of support for the MPP from the US government and the NIH, an organization with a significant patent portfolio and the world’s largest funder of biomedical research.

### **6.2 Gilead Sciences License**

The MPP reached an agreement with Gilead in July 2011. While the license has many shortcomings, it marked an important step in the MPP’s history, as it was the first agreement between the MPP and a private pharmaceutical company. In addition to containing a covenant not to enforce patents related to the ARV emtricitabine (FTC), the

---

<sup>1</sup> Tibotec is a subsidiary of Johnson & Johnson



license covered the ARV tenofovir (TDF), two ARVs in Gilead’s pipeline<sup>2</sup>—elvitegravir (EVG) and cobicistat (COBI)—and a single-pill combination of the four called the “Quad” [70]. The license grants to sub-licensees a non-exclusive right to manufacture the drugs in India and sell them in India and in certain LMICs in exchange for a 3-5% royalty payment<sup>3</sup> [71]. Under the terms of the license, sub-licensees can choose to license or not license any of the drugs covered by the license.<sup>4</sup>

In November 2011, the original license agreement was amended in response to concerns raised by civil societies and others about certain provisions [71]. The first amendment related to ambiguity regarding the non-assert provision with respect to FTC. The amendment clarified that, in the event a sub-licensee terminates the TDF portion of the license, they can continue manufacturing TDF/FTC combinations without fear that Gilead will revoke the non-assert with respect to any product containing FTC [71]. The second amendment related to a provision of the license that permits sub-licensees to supply drugs to territories outside the geographic scope of the license, which is permissible in the event an uncovered country issues a compulsory license. The original license required that Gilead and the sub-licensee be in agreement regarding the

---

<sup>2</sup> “Pipeline Products” are products that are still in development and have not yet received regulatory approval from the appropriate country authorities.

<sup>3</sup> The agreement also contained a clause in which Gilead agreed to pay the MPP 5% of all sub-licensee revenue, capped at \$1 million per year, for identifying sub-licensees and administering the licenses. However, it is unclear whether this impacted the royalty provision terms in the license.

<sup>4</sup> This is referred to as the “unbundling provision” in the license.

terms of any compulsory license; the amendment removed this provision and clarified the right of sub-licensees to supply drugs outside the covered license territories in the event a compulsory license is issued [71].

Since signing the agreement, a number of Indian generic manufacturers have engaged with the MPP,<sup>5</sup> with a notable exception of the Indian generic manufacturer Cipla. The license with the MPP was really an extension of a previous license that Gilead had for the production of TDF with a number of Indian generic companies, though the MPP was able to get much better terms than were in the previous TDF voluntary licenses.

At the same time Gilead signed its license with the MPP, it also signed additional “semi-exclusive” voluntary licenses for the pipeline products—COBI and EVG—with certain Indian generic manufacturers. These licenses contain higher royalty rates and cover sales to nine middle-income countries that were outside the geographic scope of the MPP license [12].

Gilead’s agreement with the MPP was monumental in that it paved the way for future private-sector engagement with the MPP, but it unfortunately received a lot of criticism from civil societies and access to medicines advocates, some going so far as to say that “the outcome [of the agreement] was a setback for the global movement on

---

<sup>5</sup> The following are sub-licensees: Shilpa Medicare, Shasun Pharma Solutions, Aurobindo Pharma Limited, Emcure Pharmaceuticals, Hetero Labs, and Laurus Labs.

access to life-saving medicines” [72]. Some provisions received only minor criticism,<sup>6</sup> but some have been vehemently criticized. While these criticisms may or may not be unfounded, it almost killed the MPP. There were some companies that were considering engaging with the MPP, even some that thought they would have to eventually engage with the MPP, but when the criticisms surrounding the Gilead license came out, companies became more reluctant to join the MPP [134]. These criticisms resulted in a two-year time period post-Gilead in which pharmaceutical companies refused to engage with the MPP.

The geographic scope of the license was heavily criticized because a number of important middle-income countries with high HIV burdens were excluded.<sup>7</sup> While the license explicitly states that sub-licensees can supply drugs outside the covered territories, it is only permitted if the drugs are off patent, if the country has issued a compulsory license, or if India has issued a compulsory license for export. This is problematic because, for countries that have patents on any of the drugs covered by the license, which is very likely for the pipeline products, their only option for accessing

---

<sup>6</sup> For example: a provision that prohibits parallel importation and grants to Gilead the right to terminate the license if it determines this has occurred; the fact that the MPP has no right of action to enforce the agreement; the requirement that royalties be paid for sales even in countries where there are the drugs are off-patent; and the limitation that allows only Indian generic companies to become sub-licensees.

<sup>7</sup> TDF and FTC territories include 122 countries; COBI territory includes 102 countries; EVG and the Quad territories include 99 countries. Notably excluded countries (with high HIV burdens) include: Argentina, Brazil, China, Egypt, Peru, Thailand, and Ukraine.

cheap generics is to garner the political will necessary for issuing a compulsory license, either for local production or importation from India.

The API restrictions have also received a lot of criticism. Under the terms of the license, sub-licensees can only purchase APIs from other sub-licensees or from Gilead. The result of this restriction is that Gilead is essentially ensuring that sub-licensees buy APIs from them (or one of their licensees), even if they are available elsewhere at a lower price, with the potential result that the price of APIs, and thus the final drug price, is unnecessary inflated. The license also restricts the sale of APIs by sub-licensees to only other licensees or to Gilead. This means that unlicensed manufacturers in India and other developing countries cannot buy APIs from any sub-licensees<sup>8</sup>. As a result, the ability of generic companies outside of India to obtain APIs for production of drugs covered by the license, even if they are not patented, is greatly hindered because many Indian generic companies that dominate the API market for ARVs have signed licenses with Gilead. This could potentially inflate the price of APIs, and thus generic versions of the covered drugs, worldwide. Despite the API restrictions' potential to manipulate the market for the covered medicines, the Competition Commission of India refused to find the restrictions unlawfully anticompetitive [73].

---

<sup>8</sup> In fact, part of the reason that Cipla refused to join the MPP-Gilead license was because of a pre-existing agreement with Quality Chemicals in Uganda.

While the API restrictions are problematic, the criticism was blown out of proportion. This restriction is something that the MPP really did not want, but Gilead was adamant about [74]. While this does restrict sub-licensees ability to sell APIs outside of India, the market today is by and large made up primarily of Indian manufacturers, so it is not as problematic as criticisms suggested. Also, because many sub-licensees have terminated TDF,<sup>9</sup> they can sell APIs related to TDF to anyone, and thus the API restrictions only really apply to the pipeline products.

Despite these criticisms, the MPP-Gilead license has a number of really attractive features. Under the agreement, Gilead has waived data exclusivity rights and royalties on new pediatric formulations (which can also be sold in any country, even those outside the geographic scope of the license) [70]. Gilead also allows sub-licensees to supply drugs outside the geographic scope of the license if the drug is either off patent in the importing country or the government has issued a compulsory license. The agreement grants to sub-licensees the right to terminate the license unilaterally at any time and for any reason, so that if a sub-licensee believes that any of the patents have expired or later decides they would prefer to operate outside the license, they are permitted to do so [70]. Sub-licensees also retain the right to challenge any patent covered in the license.

---

<sup>9</sup> Of the Gilead sub-licensees, Aurobindo Pharma Limited, Hetero Labs, and Emcure Pharmaceuticals Limited have terminated the TDF portion of the license. Shipla Medicare, Shasun Pharma Solutions, and Laurus Labs have retained the TDF portion of the license.

The license also contains an “unbundling” clause<sup>10</sup> that permits sub-licensees to choose which drugs it wishes to license, so that, for example, a licensee can choose to license EVG and COBI but not TDF [70]. The license also has broad field of use provisions,<sup>11</sup> which will allow the pipeline drugs to be marketed and sold for newly discovered therapeutic uses and TDF to be sold for the treatment of both HIV and Hepatitis B. Perhaps most significant is the license’s inclusion of pipeline products (EVG, COBI, and the Quad), so that as soon as these are approved by the FDA, generic versions of these new drugs can immediately enter developing-country markets.<sup>12</sup>

### **6.3 ViiV Healthcare License for Pediatric ABC**

The MPP signed its third license agreement with ViiV Healthcare on February 13, 2013 and in June 2013, Aurobindo Pharmaceuticals of India became the first sub-licensee. This license has received much less criticism than the Gilead license, partially because the terms are better, and partially because civil society groups perhaps realized that their vehement criticisms turned pharmaceutical companies off of the MPP for a while after Gilead [134]. The license covers patents related to abacavir (ABC), a WHO-

---

<sup>10</sup> This feature of the license was really important, as TDF is off patent in almost every country in the license territory, including India.

<sup>11</sup> Products containing TDF can be used for the treatment of both HIV and Hepatitis B; Products containing COBI or EVG can be used for “any use that is consistent with the label approved by the FDA or applicable foreign regulatory authority.”

<sup>12</sup> Inclusion of pipeline products is really significant because there has been a huge access problem in developing countries with respect to newer drugs since 2005 when India started patenting pharmaceuticals. Most new second- and third-line ARVs (which are increasingly needed) are patented in India.

recommended pediatric ARV for first- and second-line treatment, and grants to sub-licensee a non-exclusive, royalty-free, license to manufacture and sell both APIs and the finished products in 118 countries, in which represent 98.7% of children living with HIV/AIDS reside [75].

While the patent on ABC has expired in most countries, ViiV still has patent claims over compounds related to ABC, including a hemisulfate salt (which is patented in 65 LMICs), the pediatric formulation (which is patented in a number of countries, including India), and a combination drug with lamivudine (3TC) (which is significant because ABC is often used in combination with 3TC; while generic formulations of 3TC are widely available, ViiV still has patent claims over 3TC in a number of countries) [76]. This license has received much less criticism than the Gilead license and is a step in the right direction for the MPP.

Some terms of the ViiV license mirror the Gilead license. Like Gilead, ViiV waived data exclusivity rights under the agreement. The license contains no restrictions on challenging patents, and no restrictions on supplying to countries outside of the geographic scope of the license, provided ABC is either off-patent or the country has issued a compulsory license [77].

Despite these similarities, the ViiV license is a significant improvement over the Gilead license. Under the terms of the ViiV license, any manufacturer anywhere in the world is eligible to become a sub-licensee, unlike the Gilead agreement, which was

limited to Indian generic firms. The license also lacks the API restrictions of the Gilead license, granting to sub-licensees the freedom to manufacture and sell both APIs and finished products anywhere in the world. Additionally, whereas the Gilead license required payment of royalties (even for TDF, which is off-patent in most countries), the ViiV license is completely royalty-free [77]. The ViiV license also grants to the MPP the ability enforce the agreement, vis-à-vis both ViiV and sub-licensees. Finally, the covered license territory is more expansive than the Gilead license territory;<sup>13</sup> however, a number of countries with not insignificant pediatric HIV burdens are still excluded.<sup>14</sup>

One particularly attractive feature of the license is a grant-back provision under which any improvements developed by sub-licensees flow back to both ViiV and the MPP [77], unlike the Gilead agreement, in which improvements flowed back only to Gilead. This means that, if and when improvements are developed, the MPP can sub-license the improvements to third parties, potentially making them widely available shortly after development.

While this license is a vast improvement from the Gilead license, there are still some features of the license that are not ideal. Unlike the Gilead license, which has broad field of use coverage, the ViiV agreement allows for use of ABC only in

---

<sup>13</sup> The following countries that were excluded from the Gilead-MPP license are included in the ViiV-MPP license: Algeria, Argentina, Azerbaijan, Chile, Colombia, Costa Rica, Korea DPR, Egypt, Federated States of Micronesia, Iraq, Iran, Kosovo, Lebanon, Libya, Marshall Islands, Malaysia, Morocco, Panama, Paraguay, Philippines, Tunisia, West Bank, and Gaza.

<sup>14</sup> Most notably, China, Brazil, Russia, and Ukraine.



connection with the treatment of pediatric HIV/AIDS. While ABC currently has no other recommended uses other than treatment of pediatric HIV, any uses that may be later discovered<sup>15</sup> [2] are not covered in the license. Additionally, while the covered geographic territory is broader than the Gilead license, a number of important middle-income countries, in which 1.3% of children living with HIV/AIDS reside, are still excluded.

In addition to the license agreement, ViiV and the MPP signed a memorandum of understanding (MOU)<sup>16</sup>, in which they agreed to enter further license negotiations for pediatric HIV drugs that are in the ViiV pipeline, if and when ViiV receives regulatory approval [78]. ViiV lived up to this promise, entering into two new agreements with the MPP on April 1, 2014. Even more significant in the MOU is a stated commitment by both the MPP and ViiV to jointly seek out partnerships with third parties for the development of new FDCs needed to pediatric HIV [78]. This has the potential to be quite significant, as other pharmaceutical companies holding key patents necessary for the development of FDCs might be more amenable to collaborating with the MPP if another key player in the pharmaceutical industry is involved in the negotiations.

---

<sup>15</sup> ABC can also be used as an alternative treatment in adults, but adds complexity and cost to treatment without significant clinical advantage. Thus, it is currently only recommended for pediatric use.

<sup>16</sup> The MOU is not legally binding, but it is still significant because it publicly sets out ViiV's commitment to further collaboration with the MPP.

## **6.4 Roche Agreement**

The fourth agreement the MPP entered into was with Roche. This agreement, signed on August 5, 2013, is not a license agreement, but rather a price discount agreement for the drug valganciclovir, an oral medication for the treatment of cytomegalovirus (CMV), a viral infection affecting an estimated 10.1% of people living with HIV in LMICs [80] that can lead to irreversible blindness in people living with HIV [81]. This is significant because the only other treatment option for CMV, ganciclovir, requires a series of injections directly into the eyes that is painful, expensive, and difficult to administer on a large scale, and thus rarely sought by patients suffering from CMV [82]. The agreement was necessitated by a “vicious cycle” that currently exists with CMV—because “current treatment options are either unaffordable or inconvenient, HIV clinics rarely screen for the disease. Because clinics rarely screen for CMV, there is little demand for treatment and therefore little demand for easy to administer, affordable solutions”<sup>17</sup> [81]. As a result of this cycle, market conditions are such that there is not currently sufficient demand in developing countries for CMV drugs to facilitate generic competition through licensing. In this respect, CMV is really a ND that suffers from the same market failure as other NDs.

It is hoped that this price discount agreement with Roche, which will make valganciclovir 90% cheaper than the current price, will “scale-up the screening,

---

<sup>17</sup> Quote from Dr. David Heiden, a CMV expert working with Seva and Pacific Vision Foundations.

diagnosis, and treatment of HIV-related CMV” [83]. By reducing drug prices enough to make them readily available and affordable, a new market for valganciclovir can emerge, paving the way for the introduction of generic competition and making CMV screening a routine part of HIV care in developing countries.

Under the terms of the agreement, Roche will provide valganciclovir to non-profit HIV treatments organization—specifically, organizations financed by national governments, the Global Fund, PEPFAR, UNITAID, and MSF—and “any other similar organizations identified by the MPP and accepted by Roche” [83] at the price of 250 CHF/pack (approximately \$275USD, with each pack containing sixty tablets) [83]. This price discount is quite significant—the lowest price Roche currently offers (solely to MSF) for valganciclovir is CHF 500/pack; retail prices in most developing countries are up to ten times the CHF 250/pack price [82]. The agreement will remain in place for five years, with an option for renewal. Roche may terminate the agreement sooner, but only if there is a quality-assured generic version of valganciclovir available at a similar or lower price [83].

Under the agreement, 138 LMICs are eligible for the price discount. This is a geographic expansion from both the Gilead and ViiV agreements, but again some key middle-income countries are still excluded.<sup>18</sup> However, unlike the Gilead and ViiV

---

<sup>18</sup> Excluded middle-income countries include: Brazil, Bulgaria, China, Colombia, Mexico, Romania, Russia, and Turkey.

agreements, this agreement allows for a possible expansion of the covered territory if the MPP can demonstrate “unmet treatment needs” in any excluded country [83]. While this provision of the agreement is promising, a demonstration by the MPP of an unmet treatment need in any excluded country merely obliges Roche to enter into good faith discussions with the MPP regarding any expansion [83].

In addition to the price discount, the agreement stipulates that, in one year, Roche will enter into negotiations with the MPP for the licensing and technology transfer necessary for the development of a generic version of valganciclovir [83]. The agreement also stipulates an option for negotiations regarding a license for the ARV saquinavir (SQV), *provided that* a significant medical need for the drug is identified by the MPP [83].

Ultimately, the Roche agreement offers promise for future collaborations between the MPP and Roche for the licensing of SQV, but it remains to be seen whether Roche will take their good faith negotiation obligations seriously. By creating a market for valganciclovir, the agreement may help lay the groundwork for generic market entry, particularly since the agreement stipulates future licensing and technology transfer commitments from Roche. However, this process will take time. Thus far, there have been few purchases of valganciclovir from qualified organizations, with many more signing an acknowledgement letter for potential future purchased [74]. The impact of the agreement has not been that significant yet because in order for

organizations to purchase valganciclovir, demand for it has to increase, and that can only occur through increased screening for CMV. By making valganciclovir available at discounted prices, the MPP is paving the way for an eventual scale-up of screening and treatment of CMV. Thus, the price discount has the potential to be significant and marks a step in the right direction in providing treatment access to a treatable ND.

### **6.5 Bristol-Myers Squibb License**

The latest agreement the MPP signed, on December 12, 2013, was with Bristol-Myers Squibb (BMS). The agreement, which covers the HIV drug atazanavir (ATV), is significant in that it is the first agreement covering a WHO-preferred second-line treatment<sup>19</sup> [84]. There has been a lot of sub-licensing interest from generic manufacturers [74], but to date no sub-licenses have been signed. Prior to this agreement, BMS had agreements in place with other generic manufacturers for the manufacture of sale of ATV on a royalty-free basis, but coverage was limited to Sub-Saharan Africa and India (about fifty countries) [47]. The MPP agreement expands the geographic scope of ATV coverage to 110 developing countries that represent 88.5% of people living with HIV/AIDS in LMICs [85].

The BMS agreement contains many of the attractive features of the ViiV agreement. The agreement allows generic manufacturers anywhere in the world to

---

<sup>19</sup> UNITAID estimates that there are about 10 million people living with HIV/AIDS in low- and middle-income countries who need second-line treatments.

become sub-licensees. It also contains favorable royalty provisions, an optional technology transfer package to help facilitate sub-licensees' manufacture of ATV, and a grant-back provision that allows the MPP to sub-license any improvements or new formulations made by sub-licensees [86]. BMS also waived data exclusivity rights and granted to the MPP a right of action to enforce the agreement.

While the BMS agreement is not entirely royalty-free, the royalty provisions are interesting and different from previous MPP license royalty provisions. Like previous MPP agreements, no royalty payments are required on pediatric formulations [86], nor are they required in the countries that were covered under the previous BMS agreement or from sales made in countries where BMS does not yet have a patent *granted and in force* [86]. Thus, royalties are not required in countries where BMS has a pending patent application. Of the countries covered under the license territory, BMS has only obtained a valid ATV patent in Georgia, Pakistan, and South Africa [86]. However, because South Africa was included in the previous BMS agreement, sales in South Africa are not royalty bearing [87]. For sales in Pakistan and Georgia (and anywhere else a patent might be granted), a 3% royalty will be charged. However, the royalty will not go to BMS, but will go to the MPP, which is then mandated to "distribute [the royalties] . . . to suitable community-based HIV organizations based in the country from which royalties were collected" [86].

Like the other MPP licenses, the BMS license is not without its shortcomings. The license territory, while more expansive than the previous BMS licenses, excludes a number of middle-income countries—representing approximately 10% of the HIV burden in LMICs—are excluded.<sup>20</sup> Like the previous MPP licenses, sub-licensees can supply ATV outside of the license territory, but only if the sale does not infringe any BMS patent rights *and* the sub-licensee does not rely on the BMS technology transfer package to provide ATV [86]. Because either ATV or one or more of the APIs necessary for its production (or both) are patented in the excluded middle-income countries, their only option under the agreement for obtaining low-cost ATV is the issuance of a compulsory license. In addition to garnering the political will necessary for the issuance of a compulsory license, countries must also rely on sub-licensees' rejection of the BMS technology transfer package in their production of ATV, instead choosing to reverse-engineer ATV without help from BMS. However, should sub-licensees reject the technology transfer package, there are a number of LMICs excluded from the agreement to which sub-licensees can sell ATV because no patent is currently in force.<sup>21</sup>

---

<sup>20</sup> The license notably excludes the following middle-income countries: Argentina, Brazil, Bulgaria, China, Egypt, Indonesia, Lebanon, Malaysia, Mexico, Peru, the Philippines, Romania, Russia, and Thailand.

<sup>21</sup> Excluded countries with no ATV patent in force include: Albania, Algeria, American Samoa, Bosnia and Herzegovina, Kosovo, Jordan, Macedonia, Montenegro, Morocco, Paraguay, Serbia, Uruguay, Venezuela, and Vietnam.

Additionally, like the previous MPP agreements, the BMS license allows sub-licensees to use ATV in combination products [86]. This is particularly important for ATV because it requires boosting with ritonavir (RTV) for its effectiveness.

Unfortunately, AbbVie<sup>22</sup> holds patent rights over RTV in about twenty LMICs, some of which are within the BMS license territory.<sup>23</sup> This means that, in countries where RTV is not patented (or, if patented, a compulsory license is issued), BMS sub-licensees can not only produce cheaper versions of ATV, but also boost it with RTV—a FDC that requires only one pill a day and has few side effects. If the MPP reaches an agreement with AbbVie,<sup>24</sup> generic companies can become sub-licensees to both agreements and produce an ATV+RTV combination without any fear of infringement actions.

Should the negotiations with AbbVie fail, COBI<sup>25</sup> represents a viable alternative to RTV for combinations, as it has been shown to be as effective a booster [88]. It will be interesting to see in the future if any manufacturers that are sub-licensees of both agreements make this combination. However, there are some countries that are covered

---

<sup>22</sup> AbbVie is a subsidiary of Abbott Pharmaceuticals.

<sup>23</sup> Ritonavir is patented in the following LMICs: Albania, Armenia\*, Azerbaijan\*, Belarus\*, Bosnia and Herzegovina, Brazil, China, Kazakhstan\*, Kyrgyzstan\*, Mexico, Moldova\*, Montenegro, The Philippines, South Africa\*, Sri Lanka\*, Tajikistan\*, Turkey, Turkmenistan\*, Ukraine, and Vietnam (\* indicates inclusion in the BMS License Territory).

<sup>24</sup> The MPP and AbbVie are currently in negotiations for a license on RTV.

<sup>25</sup> Patented by Gilead and covered in the MPP-Gilead license.



under the BMS license but excluded from the COBI territory<sup>26</sup> in the Gilead license and vice versa,<sup>27</sup> so any sub-licensee's ability to sell a combination product will be subject to these geographical restrictions, barring the issuance of a compulsory license.

## **6.6 ViiV Healthcare License for DTG for Adult and Pediatric Use and ABC for Adult Use**

Shortly after signing its first agreement and a MOU with the MPP, ViiV received FDA approval for a new adult formulation, dolutegravir (DTG) [79]. The MOU signed at the time of the pediatric ABC license contained a commitment on the part of ViiV to enter into future negotiations with the MPP for pipeline products that obtain regulatory approval. ViiV honored this commitment, signing two license agreements with the MPP on April 1, 2014 covering dolutegravir (DTG) and ABC for both adult use (the "adult use license") and pediatric use of DTG (the "pediatric use license"). DTG is an important new ARV because it has fewer side effects than existing medications, is extremely potent, can be dosed once per day, does not require boosting, and has a high barrier to resistance [2]. Additionally, DTG is cheaper to manufacture than other ARVs of its

---

<sup>26</sup> The following countries are included in the ATV License Territory but excluded from the COBI License Territory: Azerbaijan, Belarus, Botswana, Costa Rica, Ecuador, El Salvador, Iraq, Kazakhstan, Korea, Democratic Republic, Libya, Marshall Islands, Micronesia, Federated States, Namibia, Panama, Sri Lanka, Turkmenistan, and West Bank and Gaza.

<sup>27</sup> The following countries are included in the COBI License Territory but excluded from the ATV License Territory: Anguilla, Aruba, Bahamas, Barbados, British Virgin Islands, Equatorial Guinea, Montserrat, Trinidad and Tobago, Turks and Caicos, and Vietnam.

class<sup>28</sup> because it contains a lower amount of APIs [136], which make up a large portion of the final cost of a drug. Furthermore, DTG can be used both as a first-line therapy in treatment-naïve patients or as a second-line therapy in patients who have developed resistance to other first-line ARVs [135].

The “adult use license” covers the manufacture and sale of DTG and ABC for use in the treatment of HIV in adults [138]. The license covers seventy-three countries—sixty-seven low-income countries, LDCs, and countries in Sub-Saharan Africa, as well as six middle-income countries, in which, collectively, 93% of adults living with HIV reside [135]. The middle-income countries covered in the license are India, Vietnam, The Philippines, Indonesia, Turkmenistan, and Egypt. This is the most limited geographic scope of any of the MPP licenses, excluding a number of important middle-income countries.<sup>29</sup>

It is disappointing that the geographic scope for ABC was not expanded to include those countries in the original ABC license for pediatric use, instead covering

---

<sup>28</sup> DTG is an integrase inhibitor.

<sup>29</sup> Excluded MICs include: Albania, Algeria\*+, American Samoa, Antigua & Barbuda, Argentina+, Armenia\*+, Azerbaijan\*+, Belarus\*+, Belize+, Bolivia, Bosnia and Herzegovina, Brazil+, Bulgaria\*+, Chile+, China\*+, Colombia\*, Costa Rica, Cuba, Dominica+, Dominican Republic+, Ecuador+, El Salvador+, Fiji+, Georgia+, Granada, Guatemala+, Guyana, Honduras+, Iran+, Iraq, Jamaica+, Jordan, Kazakhstan\*+, Latvia, Lebanon+, Libya+, Lithuania, Macedonia, Malaysia+, Maldives, Marshall Islands, Mexico\*+, Micronesia, Moldova\*+, Mongolia\*, Montenegro, Morocco\*+, Nicaragua+, Pakistan+, Palau, Panama+, Papua New Guinea, Paraguay+, Peru+, Romania\*+, Russia\*, Serbia, Sri Lanka+, St. Lucia+, St. Vincent+, Suriname, Syria+, Thailand+, Timor-Leste, Tonga, Tunisia+, Turkey\*+, Ukraine\*, Uruguay, Uzbekistan+, Venezuela, West Bank & Gaza [\* represents countries in which ViiV has obtained a patent over DTG; italicized and underlined countries and those in which a DTG patent has been filed; + represents countries in which ViiV has obtained a patent over ABC].

only those same territories included in the DTG territory. However, combinations containing ABC are not currently a WHO-recommended treatment for adults, being preferred over other first-line ARVs only in “special circumstances”<sup>30</sup> [7]. Thus, the limited nature of the geographic scope for ABC likely is not going to be problematic.

Under the license, sub-licensees can sell ABC and DTG royalty-free in Sub-Saharan Africa, low-income countries, and LDCs. In the six middle-income countries covered in the agreements, royalty payments are decided on a sliding scale based on country per capita income, with three tiers of pricing. Sales to “tier 1” countries—India, Vietnam, and the Philippines—require a royalty payment of 5%; sales to “tier 2” countries—Indonesia and Egypt—require a royalty payment of 7.5%; and sales to the “tier 3” country—Turkmenistan—require a royalty payment of 10% [138].

Within these tiers, royalty payments are only required in countries where there is a patent *granted and in force* [136]. ViiV currently has obtained DTG patents in the Philippines, Indonesia, and Turkmenistan, with patents pending in India, Vietnam, and Egypt. For ABC, ViiV holds one or more patents related to the manufacture of ABC, by itself or in combination, in Egypt, Indonesia, and the Philippines. While ViiV holds a patent over pediatric ABC in India, other patents related to ABC have been withdrawn after opposition, making it unlikely that ViiV will be able to obtain a patent over ABC in

---

<sup>30</sup> The WHO only recommends combinations containing ABC to be used for adult treatment in “special circumstances,” including “situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons.”

India in the future. It is not publicly available whether patents related to ABC are pending in Vietnam and/or Turkmenistan, but based on data provided by ViiV in the MPP license, patents are not yet in force in these countries. Because it will be a few years before generic versions of DTG and adult-use ABC will come to market, it is unclear what the effect of these royalty provisions will be in those countries in which ViiV has not yet obtained a patent over DTG and/or ABC.

Within the geographic scope of the license, further sale restrictions apply of the royalty-bearing middle-income countries. While sub-licensees can sell ABC and DTG in any market in the royalty-free license territories, the royalty-bearing license territory is segmented between the public and private markets, and sub-licensees are permitted to sell ABC and/or DTG only in the public market [138]. This includes sales to various not for profit institutions, including governments and government-run institutions, NGOs, UN organizations, not-for profit organizations (e.g. MSF, Oxfam), and funding mechanisms and programs (e.g., PEPFAR, USAID, Global Fund) [138]. Sub-licensees are required to obtain consent from ViiV before selling to any of these not for profit institutions.

The terms of the “pediatric use license” are nearly identical to the terms of the previous pediatric ABC license, with some minor improvements. The license covers 121 LMICs in which 99% of children living with HIV reside [135]. Under the license, sub-licensees have the right to manufacture and sell DTG for use in the treatment of HIV

in children ages 12-18, but the license stipulates an expansion of the field of use for treatment in children under the age of 12 if and when ViiV get FDA approval for such a formulation [137]. Like the pediatric ABC license, this license is also royalty-free. The geographic scope of the license is slightly broader, covering those countries covered in the pediatric ABC license, with Peru, Ukraine, and Venezuela added to the territory. While this still excludes some middle-income countries,<sup>31</sup> this expansion represents a step in the right direction.

Under both agreements, generic manufacturers anywhere in the world can become sub-licensees [137, 138]. Additionally, both agreements contain no restrictions on the development and formulation of FDCs. Both licenses also grant perhaps the broadest ability of all of the MPP licenses for sub-licensees to supply outside the license territory under certain circumstances. Specifically, sub-licensees are permitted to sell the licensed products outside the license territory in the following circumstances: (i) where there are no patents over the products in the country; (ii) where there are only pending patents in the country; (iii) where there are granted patents, but not infringed (e.g., the sale of DTG as a single agent where only a combination patent exists); (iv) where there is a patent in force but a compulsory license has been issued; and (v) where, under national laws, certain acts are not defined as patent infringement [136]. Additionally,

---

<sup>31</sup> Excluded MICs: Albania, Timor-Leste, American Samoa, Antigua & Barbuda, Belarus\*, Bosnia and Herzegovina, Brazil, Bulgaria\*, China\*, Dominica, Granada, Jordan, Kazakhstan\*, Latvia, Lithuania, Macedonia, Mexico\*, Montenegro, Romania\*, Russia, Serbia, St. Lucia, St. Vincent, Suriname, Turkey\*, Uruguay [\* represents countries in which ViiV has obtained a patent for pediatric DTG].

like previous MPP licenses, there is no restriction on sub-licensees' ability to challenge patents covered in the license and ViiV has waived data exclusivity.

## 7. Comparison of the MPP to Traditional Alternatives

As compared to non-assert declarations, tiered pricing, and drug donations, the MPP is far better suited to bring about long-term price reductions on ARVs, as nothing impact prices in the long-term as much as generic competition.

When compared to compulsory licensing, the MPP is an attractive alternative for both generic manufacturers and patent holders. By engaging with the MPP and increasing access to otherwise high-priced ARVs, patent holders can avert the treat of a compulsory license. The MPP similarly benefits generic manufacturers because they are able to obtain licenses on favorable terms and thus the need to resort to compulsory licensing is diminished. This is significant, as compulsory licensing not only takes a lot of political will, but also has potentially adverse side effects, both from governments and pharmaceutical companies.

A number of pharmaceutical companies already offer voluntary licenses for the patents in the MPP (Appendix A). The relevance of the MPP then is whether it can go beyond the status quo with respect to voluntary licensing, either by engaging with companies that are generally unwilling to offer voluntary licenses or widening the scope of and reducing transaction costs associated with existing voluntary licenses.

With respect to company engagement, the existence of the MPP has been an impetus for pharmaceutical companies to engage in other access initiatives. For example, Johnson & Johnson has publicly refused to engage with the MPP. However,

after refusing to negotiate with the MPP, Johnson & Johnson announced a licensing deal for rilpivirine covering the same 112 territories covered in the MPP-Gilead license.

Thus, the MPP can act an impetus for increasing access to ARVs in LMICs by encouraging companies to expand their access initiatives in other ways.

The MPP offers benefits over current voluntary licenses with respect to the formulation of FDCs. A current WHO-recommended first-line FDC consists of tenofovir (patent held by Gilead), lamivudine (GSK) and either nevirapine (Boehringer-Ingelheim) or efavirenz (BMS). An FDC of these drugs currently does not exist or is in limited supply [28], largely because generic manufacturers wishing to develop it would have to not only seek voluntary licenses from all three or four patent-holders, but would also have to negotiate the freedom to make FDCs in the license agreements. All of the current MPP licenses allow sub-licensees to develop FDCs, and thus this formulation is now possibly available to sub-licensees. Other potential combinations that will be available to sub-licensees include an ATV/COBI combination, a three in one pill that uses ABC (and two other compounds on which the patents have expired), and an ABC/3TC/DTG combination that has been shown to be potentially more effective than the current WHO-preferred single-pill first-line regimen of TDF/FTC/EVG [2].

A good point of comparison to see if the MPP is able to get better license terms as compared to traditional voluntary licenses is the 2006 Gilead voluntary licenses, which were a precursor to the MPP-Gilead license (Appendix D). While the MPP license was



basically a restatement of the previous TDF voluntary license, it offers much more favorable terms from an access to medicine perspective. While the 2006 TDF license included only 95 countries, the MPP license includes 112 countries. Even though TDF is off patent in most countries, the 2006 license restricted sales to the 95 listed territories, regardless of whether a patent was in place in other territories.

In addition to expanding the geographic scope of the TDF license, the MPP was also able to negotiate an unbundling clause that allows licensees to terminate the TDF license; the 2006 license did not allow generic manufacturers to terminate the license. Because of this unbundling provision, generic manufacturers that were tied to 95 countries in the 2006 license can drop the TDF portion of the MPP license and sell to any country in the world. This is really significant because TDF is one of the most important first-line ARVs in existence today. The MPP license also has lower royalty rates—3% as compared to the 5% royalty rate in the 2006 licenses.

Additionally, as compared to other voluntary licenses for ATV, the MPP-BMS license covering ATV offers much more favorable terms. Under a 2011 voluntary license between BMS and Mylan pharmaceuticals, Mylan was granted a non-exclusive right to manufacture and sell ATV in certain undeveloped countries—only India and Sub-Saharan Africa—on a royalty-free basis. The license contains an anti-diversion clause that prohibits Mylan from selling ATV outside of certain territories, in countries where BMS has a patent or a *pending patent*, and gives BMS a rescission right if Mylan breaches

this clause. This is in contrast to the MPP license, which prohibits sales only in countries where BMS has been *granted* a patent, and does not give BMS a rescission right in the event that ATV is sold outside the license territory. The MPP license also has a much more expansive geographic scope, allowing for sale in 110 countries as opposed to the fifty countries covered by BMS voluntary licenses. Also, in an agreement between BMS and Brazil, BMS prohibited Brazilian manufacturers from boosting ATV with ritonavir [2]. This is in contrast to the MPP agreement, which allows for combinations.

## **8. Is the MPP better than the Alternatives?**

With respect to some alternatives—non-assert declarations, tiered pricing, and drug donations—the MPP is better because it allows for generic competition in the marketplace for ARVs, which is more effective than any other mechanism at bringing down prices and making medicines more widely available.

With respect to voluntary licensing, the MPP offers clear advantages over the status quo. By negotiating with patent holders from a public health perspective, the MPP aimed, and succeeded, in negotiating better terms than what was contained in existing voluntary licenses, with the result that more countries will benefit from the licenses, and the countries that were already benefitting from voluntary licenses will benefit on better terms. The MPP has not only been able to expand the geographic scope of the licenses, but also increase the number of licensees able to produce generic versions of licensed products, thereby increasing competition and potentially lowering the prices of ARVs. The MPP licenses have also been able to give sub-licensees the right to challenge patent applications and supply licensed products in countries where the drug is off patent or the country has issued a compulsory license. Perhaps most importantly, the MPP has granted to sub-licensees the ability to formulate new FDCs that contain the licensed drugs, which previously was often not an option for licensees under voluntary licenses.

The MPP has also been able to facilitate licenses of pipeline products and new ARVs, which will be available cheaply much sooner than what would otherwise be a 20-year patent term. This has not had an impact yet in terms of increasing access, but is nevertheless important because it will reduce the timeline for generics being on the market, allowing for more rapid price reduction. However, the pipeline drugs included in the Gilead agreement have only recently obtained regulatory approval in the US, and generic companies have only just started to develop generic versions of these ARVs. Likewise, DTG has only recently received regulatory approval in the US. Because the process for drug development takes time—generic manufacturers have to develop the API and then the finished formulation—it will be a couple of years before a generic version can even be submitted for regulatory approval, after which it will be another six months to a year before the drug actually comes to market. However, this two to three year timeline is certainly better than the usual twenty-year plus timeline.

It is also too early to tell what the impact of the MPP will be with respect to the development of new FDCs. With respect to the MPP's ability to stimulate the development of new formulations, it is too early to tell whether or not it has been successful. An MPP sub-licensee has started working on the development of a three-in-one pill that includes ABC and two other compounds on which the patents have expired. The MPP was able to facilitate this, however it will be at least few years before any new FDC to materialize. Another potential combination that has been proven

effective at treating HIV is an ATV/COBI combination (with COBI as a booster, rather than historically-used booster ritonavir, which is patented by AbbVie in a number of LMICs). Because both of these drugs are licensed to the MPP, sub-licensees wishing to develop this formulation only have to go to one place—the MPP—to obtain formulation rights, rather than negotiating individually with BMS and Gilead for the rights. A previous BMS voluntary license for ATV prohibited licensees boosting ATV with ritonavir [2], and it is not public knowledge whether previous Gilead licenses restricted the development of combination products. It is thus possible that individual voluntary licenses for these two compounds would have prohibited the development of an ATV/COBI combination, which is clearly permitted under both MPP agreements. In this way, the MPP has the potential to foster the development of FDCs that may otherwise not exist in generic form before the expiration of the patent term, particularly FDCs containing newer ARVs that may be patented in India.

The MPP has also been a valuable tool in promoting access to ARVs even outside the context of the MPP. As seen with the 2011 Johnson & Johnson license for riplivine, the mere existence of the MPP can serve as an encouragement for pharmaceutical companies to expand their access initiatives.

It is clear that the MPP is a vital component of the overall strategy to increase access to ARVs globally. However, the MPP should be used in concert with other initiatives, especially in the near future when generic products of newer drugs are not

yet on the market. In addition, there need to be policies in place in LMICs that improve the overall health infrastructure in countries. Without these efforts, there will always be patients without access to treatment, regardless of how inexpensive or widely available they are.

## **9. R&D Efforts for NDs**

### **9.1 *The ND R&D Landscape***

Historically, there has been little investment in R&D aimed at developing new treatments for NDs. From 1975 to 1999, only sixteen of the 1,393 new chemical entities marketed were for NTDs [89] and tropical diseases accounted for only 1.5% of all biomedical citations on PubMed [90]. Because patent protection is the primary policy tool that drives R&D investments, until the early 2000s, only 0.5% of pharmaceutical patents were for drugs aimed at treating NDs [90].

During this time, less than 10% of global health R&D expenditure was spent on health problems affecting the developing world, which represented more than 90% of the world's global disease burden [91]. This phenomenon came to be known as the "10/90 gap." Recognition of this gap in the late-1990s led to the establishment of the Global Forum for Health Research, which aimed to help narrow the gap by facilitating collaborations between partners in both the public and private sectors [90]. While this gap has decreased since the 1990s, North America and Europe still make up 80% of the global market for drugs, so drug development globally remains primarily focused on the needs of developed nations, resulting in disproportionate development of "lifestyle drugs" and drugs for non-communicable diseases [18].

However, since the early 2000s, there has been increasing interest in NDs, and a number of initiatives that aim to address the issue and incentivize investment in R&D

for NDs have come to life. This has been brought about by a dramatic increase in funding for R&D for historically neglected diseases, primarily from the NIH<sup>1</sup> and the Bill and Melinda Gates Foundation [139]. Because of increased funding for ND R&D by donor organizations and governments over the past two decades,<sup>2</sup> over 140 ND products are now in development, from a baseline of almost zero pre-2000s, and in 2009 alone there were 69 drugs, vaccines, and diagnostics in the pipeline for NDs (excluding HIV) [92]. This has been spurred largely by the proliferation of product development partnerships (PDPs) and other public-private partnerships and initiatives on behalf of governments and pharmaceutical companies to address the ND problem. Nevertheless, ND R&D funding remains small compared global funding for R&D in the pharmaceutical industry generally, representing only about 2% of total funding [93].

Despite the recent increase in ND R&D funding, there remains, in addition to a disparity between health R&D that is needed (based on global disease burden) and that which is undertaken, a disparity between R&D expenditure within the ND category. While some NDs receive significant amounts of global ND R&D funding, others receive virtually no funding, often with little correlation to global disease burden (Table 1). This can likely be explained by the fact that diseases such as HIV/AIDS, TB, and malaria (which account for over 4.3 million deaths annually) have developing-country markets,

---

<sup>1</sup> The NIH is by far the largest funder of ND R&D, providing about 40% of global funding in 2007.

<sup>2</sup> Global estimated funding for ND R&D in 2010 was about \$3 billion



despite primarily affecting those living in LMICs, and thus there is more of an incentive for pharmaceutical companies to engage in R&D. As compared to diarrheal diseases and pneumococcal disease (which claim about 3.8 million lives annually), HIV/AIDS, TB, and malaria have four times the number of R&D projects currently [94].

**Table 1: Percentage of Global Neglected Disease R&D Funding**

Disease	Global Disease Burden (DALYs)	Total Global ND R&D Funding
HIV/AIDS	57.8 million	33.8%
Tuberculosis	34 million	17.3%
Malaria	33.9 million	18.4%
Dengue	663,000	7.5%
Diarrheal Disease	72.3 million	5.0%
Kinetoplastids	4.1 million	4.3%
Bacterial pneumonia & meningitis	93.3 million	3.2%
Helminth infections	12 million	2.7%
Salmonella infections	22 million	1.5%
Trachoma	1.3 million	0.3%
Leprosy	194,000	0.2%
Buruli ulcer	*	0.2%
Rheumatic fever	5.1 million	0.0%

\*No DALY figures are available, but the WHO estimates that Buruli Ulcer affects more than 7,000 people each year

The current patent landscape for compounds and technologies related to NDs is scattered, with a number of different stakeholders—pharmaceutical companies, universities, smaller biotechnology companies, governments, and PDPs—all owning patents related to NTDs. These parties also have important trade secrets covering data and know-how related to NDs, which is arguably more important than the patents

themselves. There is thus a pressing need to increase both funding and efficiency of ND R&D, as funding and disease focus is scattered and there are often several efforts targeting the same outcomes running in parallel with little exchange of information.

## **9.2 ND R&D Collaborations**

The increase in ND R&D has been spurred by the proliferation of collaborative efforts between the non-profit and for-profit sectors. These initiatives bring together funding and/or expertise from governmental, inter-governmental, and non-profit organizations and funding and/or expertise from the for-profit sector [90]. The partners in these collaborations are varied, ranging from international organizations (e.g. WHO), public institutions (e.g. NIH), and private foundations (e.g. the Rockefeller Foundation) to the private actors in the pharmaceutical industry, and, in addition to providing R&D funding, these organizations often directly support basic ND research [90].

### **9.2.1 Product Development Partnerships**

Product Development Partnerships (PDPs) represent perhaps the most significant type of these collaborations. PDPs aim to coordinate the development of new ND drugs, vaccines, diagnostics, and other technologies. By working with the public sector, donor organizations, and pharmaceutical companies, which provide funding and other resources, PDPs are able to initiate ND R&D that otherwise would not be undertaken [37]. In addition to product development, many PDPs simultaneously

engage in global advocacy work aimed at increasing awareness of their targeted NDs [95].

PDPs have played a significant role in ND R&D, accounting for upwards of 75% of all NTD R&D and attracting over 40% of global ND R&D funding [95]. However, PDPs focusing on HIV/AIDS, TB, and malaria receive by far the most funding. Notable exceptions to this are the \$25.6 million PATH received for the development of a vaccine against diarrheal disease and the \$22.7 million DNDi received for the development of kinetoplastic drugs [95].

While all PDPs ultimately share the common goal of increasing R&D for NDs, they vary significantly with respect to disease and product focus (Table 2), with some focusing on a single disease or single product, and others focusing on a range of diseases and/or products. Additionally, some PDPs concern themselves only with product development, while others engage in a variety of technology transfer and capacity-building initiatives [95].

**Table 2: Various PDPs, with Disease and Product Focus**

PDP	Disease Focus	Product Focus
Aeres Global TB Vaccine Foundation	TB	Vaccines
Drugs for Neglected Diseases Initiative (DNDi)	Malaria, kinetoplastids (sleeping sickness, Chagas, and leishmaniasis)	Drugs
European Malaria Vaccine Initiative (EMVI)	Malaria	Vaccines
Foundation for Innovative New	TB, malaria, sleeping	Diagnostics

Diagnostics (FIND) Global Alliance of TB Drug Development (TB Alliance)	sickness TB	Drugs
Infectious Disease Research Institute (IDRI)	HIV, TB, leishmaniasis, leprosy	Vaccines, diagnostics
Institute for One World Health (iOWH)	Malaria, leishmaniasis, diarrheal diseases	Drugs
International AIDS Vaccine Initiative (IAVI)	HIV/AIDS	Vaccines
International Partnership for Microbicides (IPM)	HIV/AIDS	Microbicides
International Vaccine Institute (IVI)	Diarrheal disease, dengue, bacterial pneumonia and meningitis, typhoid and paratyphoid fever	Vaccines
Medicines for Malaria Venture (MMV)	Malaria	Drugs
Program for Appropriate Technology in Health (PATH)	HIV, malaria, rotavirus and other diarrheal diseases	Vaccines, microbicides, diagnostics
Sabin Vaccine Institute	Helminth diseases (Hookworm and Schistosomiasis)	Vaccines
WHO-Special Programme for Research and Training in Tropical Diseases (WHO-TDR)	TB, malaria, kinetoplastids, helminth diseases, dengue	Diagnostics, drugs

*Source: Moran et al., "The Role of Product Development Partnerships in Research and Development for Neglected Diseases"*

PDPs are further differentiated from one another with respect to organizational structure and reliance on external partners for R&D. Some PDPs are independent organizations,<sup>3</sup> while some are programs set up within larger organizations.<sup>4</sup> With

<sup>3</sup> For example: Aeras Global Vaccine Initiative and Medicines for Malaria Venture.

<sup>4</sup> For example: MVI, the Meningitis Vaccine Project hosted by PATH, and the Pediatric Dengue Vaccine Initiative, hosted by IVI.

respect to R&D activities, some PDPs have their own labs and manufacturing plants, while others are fully reliant on external partners for these activities [95].

Despite these organizations differences, the activities of PDPs have been highly influential, spurred by the relative low costs PDPs require to develop products, from the drug development stage to the clinical trial phase, as compared to pharmaceutical companies. Though estimates vary and remain controversial, the average private-sector cost to develop a new drug has been estimated as high as \$1.3 billion [96]. PDPs have been able to similarly develop products at a fraction of the price. For example, between 2003-2011, DNDi was able to build a significant pipeline of products and develop six new products<sup>5</sup> with an investment of just EUR100 million; over a ten year period, and MMV built a pipeline of sixty products and developed three new products<sup>6</sup> with a budget of just \$310 million [93]. Another advantage of PDPs is that, because of their public health focus, they are able to push pharmaceutical companies contributing patents and know-how to keep the products they develop off patent, as was seen in the case of the antimalarial FDC ASAQ, developed by DNDi [37].

While PDPs have played a monumental role in changing the ND R&D landscape, they cannot solve the ND problem alone. PDPs are heavily dependent on donations for funding their operations, with many funded primarily by a few donor organizations.

---

<sup>5</sup> Including five combination treatments for malaria, sleeping sickness, and visceral leishmaniasis, and a pediatric formulation for Chagas.

<sup>6</sup> Including a pediatric formulation, injectable artesunate, and a new FDC.

Funding is extremely concentrated, with five organizations<sup>7</sup> accounting for almost 80% of all PDP funding and the Gates Foundation alone providing almost 50% [95]. This means that if even one donor for a particular PDP were to cut or cease funding, the entire operation would be jeopardized. This is particularly relevant for PDPs that are moving to the clinical trial stage of drug development, which is significantly more expensive than the initial R&D stages.<sup>8</sup>

Additionally, there is currently a lack of sources tracking ND R&D among various initiatives, a lack of sharing of clinically relevant knowledge and data, and a lack of coordination of donor funding [97]. Because PDPs compete with one another for funding, there is little incentive for them to coordinate their research efforts with one another with respect to both successful and failed efforts, and as a result there is a lot of duplication among PDPs focusing on the same disease [37], which increases the cost and timeline associated with ND R&D.

PDPs are also heavily dependent on pharmaceutical companies for access to compounds, data, and infrastructure necessary to conduct R&D. While IP barriers have not been a huge problem with PDPs in the past [12], their efforts depend on the on-going goodwill of pharmaceutical companies to offer access to this type of information.

Additionally, although PDPs focus their efforts on diseases primarily affecting LMICs,

---

<sup>7</sup> The Gates Foundation, USAID, the UK Department of International Development, the Dutch Ministry of Foreign Affairs, and Irish Aid.

<sup>8</sup> Clinical trials represent as much as 60% of total drug development costs.

there is little engagement with governments and people actually living in LMICs, with 87.8% of PDP R&D funds being reinvested into Western academic institutions, contractors, and pharmaceutical companies [95]. As many scholars have noted, “not one global PDP is led by a person who is a developing-country national and not one resides within one of the developing countries severely affected by neglected infectious diseases” [98]. Thus, their efforts may not reach their potential with respect to addressing problems most pressing to LMICs.

### **9.2.2 Other ND R&D Collaborations**

Pharmaceutical companies, in addition to involvement in PDPs, have become active in ND R&D in other ways, such as opening their own ND R&D facilities (Appendix E), donating drugs to LMICs, making their compound libraries available to various open source initiatives, and various other one-off collaborations aimed at increasing access to ND drugs and R&D.

A notable example of one such collaboration is the case of Merck and the river blindness drug Mectizan. Merck spent million of dollars developing the drug throughout the 1990s, before which there was no cure for the disease. Merck collaborated with the WHO, the World Bank, and other NGOs to distribute free doses of Mectizan to those suffering from river blindness in various LMICs, mostly in Africa. It is estimated that these efforts have spared sixteen million children from river blindness and have prevented over 600,000 cases the disease [31].

Other collaborations include a partnership between Novartis and iOWH that gave iOWH access to proprietary research data for the development of a diarrhea drug; a collaboration between Novartis and the Institute for Microbiology and Epidemiology in Beijing for the development of an antimalarial drug; a Pfizer initiative in Africa aimed at eliminating trachoma [31]; and a collaboration between GSK, the University of Liverpool, the Wellcome Trust, and the UK Department for International Development, all of whom collaborated to develop a new first-line antimalarial drug, LAPDAP, that is currently in late-stage clinical development [90]. This small sample of collaboration efforts is nowhere near exhaustive, and represents only a few of the various private sector, public sector, and non-profit initiatives aimed at increasing ND R&D.

A number of collaborations for drug repurposing have also come to life. The NIH National Center for Advancing Translational Sciences (NCATS) is one such initiative. Like other drug repurposing initiatives, NCATS aims to foster collaboration between academic institutions and pharmaceutical companies to find new uses for old compounds on which no research is currently being conducted. To date, a number of pharmaceutical companies have signed on to the initiative,<sup>9</sup> making fifty-eight different compounds available to academic institutions [99]. NCATS and other drug repurposing initiatives add to the ND R&D landscape significantly, as the compounds have already undergone initial stage R&D and testing.

---

<sup>9</sup> Pfizer, AstraZeneca, Eli Lilly, Abbott, BMS, GSK, Janssen Pharmaceuticals, and Sanofi



## **10. WIPO Re:Search Consortium**

While PDPs and other collaborations have facilitated broader ND R&D, they are often fragmented, ad hoc, insufficient [93], and/or rely heavily on funding that may or may not be available in the future. The World Intellectual Property Organization's (WIPO) Re:Search Consortium hopes to overcome these shortcomings by offering an innovative solution to sharing IP and other technologies and know-how related to ND R&D.

### ***10.1 History of WIPO Re:Search***

In 2009, pharmaceutical company GSK founded the Pool for Open Innovation against Neglected Tropical Diseases and placed 500 patents and 300 pending patents in the Pool in hopes that access to this information would help others more rapidly develop potential medicines for NTDs [105]. Spearheaded by GSK CEO Andrew Witty, the vision of the Pool was to make IP related to NTDs—small molecule compounds and/or process patents—available for free to researchers and developers pursuing R&D aimed at treatments for NTDs [106]. Witty recognized the need to make NTD-related IP freely available because the lack of a market incentive for the development of NTD drugs resulted in an unwillingness on the part of pharmaceutical companies to engage in R&D for NTDs [106]. Witty felt that the real value of the Pool would be in the form of “enabling technologies, data, maybe failed trials or other things [GSK has] done that

failed, all of which would make it easier for others to build on the foundations of what has already been achieved or tried" [106].

A year after the Pool was formed, GSK had granted free licenses to more than 800 patents on NTDs and had made available data it had generated on 13,500 antimalarial compounds. GSK was also able to engage with Alnylam pharmaceuticals, which donated an additional 1,500 patents in the Pool, and the Massachusetts Institute of Technology, which contributed IP rights and know-how related to NTD research. Despite these contributions, the Pool achieved limited success, leading to only one publicly disclosed partnership between GSK, iThemba Pharmaceuticals, and the Emory Institute of Drug Discovery, working together to develop targets for latent-state TB [107].

This limited success was likely attributed to the fact that the pharmaceutical industry was perceived to be solely a GSK initiative. In 2010, the Pool was transferred to BioVentures for Global Health (BVGH), and again transferred to WIPO in October 2011 and renamed WIPO Re:Search Consortium.

With the transfer of the Pool to WIPO, a number of changes were implemented. Re:Search expanded the focus of the Pool for Open Innovation to cover more diseases and to incorporate patents for vaccines and diagnostics in addition to drug patents [12]. Re:Search also implemented a policy that requires innovators to make any future products available in LDCs on a royalty-free basis [12].

## **10.2 Overview of Re:Search**

The aim of Re:Search is to accelerate the discovery and product development of drugs, vaccines, diagnostics, and other technologies related to NTDs, TB, and malaria by embracing an “open innovation framework for the sharing of intellectual property, and technology and research materials not protected by intellectual property rights” [108]. By providing researchers with access to not only the IP for pharmaceutical compounds and technologies, but also know-how and data for R&D for NTDs, TB, and malaria, Re:Search hopes to stimulate the development of new, better treatment options for NTDs [109]. This is significant because much of the data and know-how that is essential for drug discovery, though not patented, is not publicly available. Providing researchers with this “intellectual capital, including screening hits, expertise, and know-how” [107] can potentially facilitate more rapid and efficient drug discovery.

Re:Search also aims to facilitate technology transfer and capacity building in developing countries. It hopes to do this through a Funds-in-Trust grant that enables scientists from developing countries and LDCs to take “sabbaticals” at research facilities in developed countries [109].

Re:Search Members are comprised of institutions from the public and private sectors, as well as academic institutions and civil societies. “Providers”<sup>1</sup> are Members

---

<sup>1</sup> Current Providers are: Aberystwyth University; African Institute of Biomedical Science and Technology; Alnylam; Biotech; Caltech; Center for Excellence for Malaria Diagnosis, University of Lagos, Nigeria; Center for World Health & Medicine; DNDi; Eisai; Eskitis Institute, Griffith University; FIND; Fundacao Owealdo

that contribute IP, materials, or services into the pool for license or use, and “Users,”<sup>2</sup> which can be anyone (e.g. academic institutions, researchers, PDPs, and pharmaceutical companies) with a commitment to improving access to NTD medicines in LDC, are those Members that have entered into license agreements with Providers to use the IP and other materials donated to the pool. Re:Search also have a number of “Supporters”<sup>3</sup> that encourage the facilitation of NTD R&D.

Re:Search has three components to it: (1) a Database, which provides Users with details of IP available for licensing, as well as services and other technology or materials not necessarily protected by IP rights which can be accessed by Users; (2) a Partnership

---

Cruz (Fiocruz); GSK; Infectious Disease Research Institute; Institut Pasteur Korea; Institute Pasteur de Tunis; International Centre for Genetic Engineering and Biotechnology; International Federation of Intellectual Property Owners; IVI; iThemba; Kenya Agricultural Research Institute; Kusami Center for Collaborative Research, Ghana; Liverpool School of Tropical Medicine; Mass General Hospital; MIT; McMaster University, Canada; McGill University; Medical Research Council, South Africa; MMV; Merck; Murdoch Children’s Research Institute; NIH; Nigerian Institute of Medical Research; Northeastern University; Novartis; Pfizer; PATH; Sanofi; Seattle Biomed; 60 Pharmaceuticals; Stanford; Swiss Tropical and public Health Institute; National Institute of Immunology, India; Noguchi Memorial Institute for Medical Research, University of Ghana; Theodor Bilharz Research Institute; Tulane; University of Bamako, Mali; University of British Columbia; University of Buea, Cameroon; Berkeley; University of Dundee; University of Ibadan, Nigeria; University of Kansas; University of Vermont; University of Washington; Walter Reed Army Institute of Research.

<sup>2</sup> Current Users include: many providers (DNDi, Fiocruz, MMV, MRC, among others), as well as Anacor; Emory University; GALVmed; Sabin Vaccine Institute; University of Calgary; UCSF.

<sup>3</sup> Current Supporters include: Africa Fighting Malaria; Association of University Technology Managers; BIO; Council on Health Research for Development; Developing World Health; European Commission – Directorate General for Research and Innovation; Indian Council of Medical Research; IFPMA; International Hospital Federation; Kenya Medical Research Institute; Licensing Executive Society International; Mahidol University; National Institute of Industrial Property, Brazil; Public Interest Intellectual Property Advisors; Tech Transfer Summit Ltd; USPTO.

Hub, managed by BVGH, where Members and other interested parties can learn about Re:Search, available licensing and research collaboration opportunities, networking possibilities, and funding options; and (3) a range of supporting activities (e.g. facilitating negotiations of licensing agreements and identifying research needs and opportunities) [108].

The focus of Re:Search is on obtaining patents, data, and know-how related to TB, malaria, and twenty-three NTDs.<sup>4</sup> Re:Search seeks IP related to drugs,<sup>5</sup> vaccines,<sup>6</sup> and diagnostics<sup>7</sup> that are or may be relevant for NTD treatments. Providers contribute IP, data, and know-how related to NTDs, which is then put into the Database. Any interested party can search the Database—by data type, Provider, or disease focus—for “compounds, unpublished scientific results, patents and patent rights, screening and platform technologies, and regulatory dossiers” [110]. If a researcher finds something in

---

<sup>4</sup> Buruli Ulcer; Chagas disease (American trypanosomiasis); Cysticercosis; Dengue/dengue hemorrhagic fever; Dracunculiasis (guinea-worm disease); Echinococcosis; Endemic treponematoses (Yaws); Foodborne trematode infections; Clonorchiasis; Opisthorchiasis; Fascioliasis; Paragonimiasis; Human African trypanosomiasis; Leishmaniasis; Leprosy; Lymphatic filariasis; Onchocerciasis; Rabies; Schistosomiasis; Soil transmitted helminthiasis; Trachoma; Podoconiosis; and Snakebite.

<sup>5</sup> This includes: compounds with ND data (known activity against NTDs); compound libraries from other projects (drug targets for other diseases/conditions); other compounds of potential interest in NTD research; technologies or drug target identification and validation, high throughput screening, or complex dataset analysis; technologies for drug formulations or drug administration.

<sup>6</sup> This includes: existing or novel adjuvants for vaccines; viral, DNA, or bacterial vaccine vectors; vaccine delivery technologies; cold chain/stability solutions for vaccines; clinical trial data or patient samples from ND vaccines in development.

<sup>7</sup> This includes: validated biomarkers; detection methods; platform technologies; patient samples from ND diagnostics in development.

the Database that interests them, they then contact BVGH—the administrator of the Partnership Hub—for more information regarding licensing. BVGH works to match the User with the Provider, who then develop their own research collaboration [110].

With one of the aims of Re:Search being new product development, IP issues will invariably arise with respect to both the inputs from Providers and outputs by Users. With respect to the management of IP, Re:Search mandates that Providers grant Users royalty-free licenses for R&D and manufacture of technologies to sell in LDCs [108]. Users retain IP rights in any innovation generated through the Re:Search collaboration, but must commit to providing any products born out of these collaborations to LDCs on a royalty-free basis, and to negotiate with other developing countries on a case-by-case basis, with public health goals in mind [108]. While Providers cannot claim any IP rights from Users for future products developed, they can require that Users do not assert IP rights against them for any future research or product development [108].

### ***10.3 Theoretical Benefits of Re:Search***

The overall goal of Re:Search—and the overall benefit that will stem from it—is a faster rate of ND drug innovation, which “can be achieved through radical innovation springing from openness, connectivity, flexibility, and adaptability” [111]. While there are many PDPs currently working on R&D for NDs, there are “more researchers and projects that could benefit from the IP and knowledge of biopharmaceutical companies, research institutions, and universities” [109]. Recognizing this need for further

collaboration, Re:Search hopes to make greater progress in ND R&D beyond what PDPs have accomplished. By offering researchers and PDPs access to IP related not only to patents, but also related data, technologies, and know-how, Re:Search has the potential to be a driving force for innovation in the discovery and development of new drugs and reduce the costs associated with drug development [12].

There are currently a number of other open source and database initiatives<sup>8</sup> aimed at ND R&D, but these initiatives are often focused on a particular disease, restricted to patents, and/or geographically limited. Re:Search expands the efforts of these other open source initiatives by broadening and diversifying the scope of the initiatives, encouraging participation from researchers around the world and from a number of different sectors, and expands the information in the database well beyond patents. Additionally, by providing a publicly searchable database of available IP and other resources, Re:Search can go beyond other open source and database initiatives by facilitating new partnerships that would otherwise not be facilitated [112].

Re:Search has the potential to speed up the development of new drugs for the treatment of NTD, TB, and malaria by increasing access not only to IP, but also to research tools, screening infrastructure, technologies, data, and know-how, which should facilitate a more rapid development of new compounds for the potential

---

<sup>8</sup> Examples of such open source collaborations include: Open Source Drug Discovery; open compound databases such as CDD and PubChem; the Tropical Disease Initiative; and TDR Targets.

treatment of diseases such as TB and malaria [113]. Such sharing of data and know-how can “take out some of the error from the trial-and-error process of drug discovery” [107] by providing researchers with knowledge about “what’s worked before and what hasn’t worked” [107]. The drug development process may also be accelerated by Re:Search’s potential to lower the transaction costs and time associated with locating and licensing multiple patents, which can be overly-burdensome for some research organizations. Re:Search is able to do this by taking a very proactive approach to forming new collaborations. When a new member wishing to engage in ND R&D joins Re:Search, BVGH visits their headquarters, learns about their research, and inquires as to what could help move their help move their research forward. BVGH then looks across their network to see which Members may have the assets these researchers seek, ultimately linking two parties that would otherwise not have collaborated [140].

Because product markets for ND treatments are small, patent holders often do not have much of an incentive to withhold IP related to ND treatments. Thus, access to IP is not necessarily the most important benefit that that Re:Search offers to researchers engaged in ND R&D. However, in the case drugs and technologies that are used to treat diseases endemic in developed-countries but simultaneously have known or potential therapeutic benefits for NTD treatments, access to IP is important. Additionally, for NDs that have a developed-country market (e.g. TB, malaria, Chagas), access to patents and know-how is similarly important.



Because access to patents may not be important for some ND R&D, the real benefit of Re:Search in these cases is not so much in providing access to patents, but in providing access to data and know-how that may not be protected not by patents but is nevertheless not publicly available. Access to this type of data and know-how is critical for early stage development, as it is necessary in order to determine what compounds merit further testing [12]. Another benefit of Re:Search is the forging of new partnerships between organizations that carry out research on treatments of NTDs [111], particularly researched institutes located in developing countries and LDCs, which are most attuned to the ND landscape.

#### ***10.4 Re:Search so Far***

The current Re:Search network involves pharmaceutical companies, smaller biotechnology companies, PDPs, universities, and research institutes, both in developed and endemic countries, who have all come together to help each other through licensing agreements and other collaborations. As of February 2014, forty-six agreements had been signed among eighty members granting access to patents, data, know-how, and other technologies related to ND R&D (Appendix F).

Re:Search has also facilitated five “sabbatical” collaborations where researchers from developing counties and LDCs have gone to research institutes in developed countries, a level of collaboration that is not seen in PDPs. These sabbatical arrangements, which aim to facilitate technology transfer and capacity building in

developing countries and LDCs, have allowed scientists in Africa to work with top researchers and industry players in developed countries. These scientists can take what they learn in these collaborations back with them to their home countries and implement what they have learned, thus fostering greater ND R&D in the countries actually impacted by NTDs, TB, and malaria. To date, five sabbatical arrangements have started, involving scientists from Cameroon, Egypt, Ghana, Nigeria, and South Africa, who have gone to R&D facilities at pharmaceutical companies (Novartis and AstraZeneca) and universities (Stanford University and the University of California-San Francisco) [114].

In addition to these agreements, a number of Providers have contributed to the Database. Contributions have come in many forms, have been made by pharmaceutical companies, PDPs, universities, and research institutions, and have covered a range of diseases (Table 3).

**Table 3: Contributions to the Re:Search Database**

Type of Data	# Documents	Diseases Covered
Screening or Hits data	7	TB, malaria, Chagas, HAT
Hit-to-Lead Data	4	Leishmaniasis; malaria; TB; HAT
Lead Series	7	Leishmainiasis; Chagas; HAT; malaria; foodborne trematode infections; lymphatic filariasis; Onchocerciasis; Schistosomiasis; soil transmitted helminthiasis; Cysticercosis; guinea worm disease; Echinococcosis; Yaws
Pre-Clinical Candidate	7	Chagas; leishmaniasis; 6 unknown
Clinical Candidate	0	
Marketed Products	6	HAT; leishmaniasis; malaria; TB
Enabling Technology Platforms	8	Leishmaniasis; malaria; dengue; Buruli; leprosy; lymphatic filariasis; Onchocerciasis;

IP (patents)	91	Podoconiosis; rabies Malaria; TB; 15 unknown; dengue; trachoma; leishmaniasis; lymphatic filariasis; rabies; Buruli; leprosy; Onchocerciasis; Schistosomiasis; Chagas; HAT; Podoconiosis; snakebite; soil transmitted helminthiasis; Cysticercosis; guinea worm disease; Echinococcosis; Yaws; foodborne trematode infections
Formulations	0	
Diagnostic Tool	3	Malaria; dengue; Buruli; leishmaniasis; leprosy; lymphatic filariasis; Onchocerciasis; Podoconiosis; rabies
Vaccine Technology	3	Malaria; dengue; rabies; Chagas; TB
New Biological Entity	0	
Other Data, Know-How, Services, or Resources	47	Malaria; Schistosomiasis; HAT; Onchocerciasis; soil transmitted helminthiasis; leishmaniasis; TB; 12 unknown; lymphatic filariasis; Chagas; Buruli; leprosy; Podoconiosis; rabies; snakebite; trachoma; Cysticercosis; dengue; guinea-work disease; Echinococcosis; Yaws; foodborne trematode infections

BVGH has also started a “Funders Database,” which lists all open funding opportunities relevant to ND research. The database “summarizes and categorizes funding opportunities' critical information, including program description, disease and product focus, stage of R&D, researcher and institute eligibility requirements, geographic restrictions, deadline, contacts, and URL” [115].

## **11. Does Re:Search Make a Positive Difference in Facilitating ND R&D?**

It is clear that, because of the nature of ND R&D and the lack of market incentives that exist to facilitate it, no single no incentive scheme or innovative financing model can address all of the challenges currently surrounding R&D for NDs. PDPs have played an important role in facilitating ND R&D, but their efforts are often fragmented and/or have a narrow disease or product focus. Additionally, there are many research efforts being undertaken at academic institutions around the world, and these efforts can provide insights to PDPs and complement their work, thereby potentially speeding up ND drug development, but researchers and PDPs often are not aware of one another's efforts, and thus collaborations often do not come to fruition [140]. Re:Search is attempting to solve this problem, complementing the initiatives of PDPs by forming collaborations between researchers PDPs who may be able to provide insight and guidance to one another in ND drug development [140].

Re:Search has, to date, made a significant contribution to ND R&D, complementing the efforts of PDPs and other open source collaborations. Open sharing of knowledge and information is absolutely necessary for ND R&D, because without it, transaction costs remain high and many are unable to engage in ND R&D. Additionally, Re:Search has been able to foster partnerships that would otherwise have not come to fruition, particularly with respect to technology transfer and capacity building within

LMICs that is being fostered through the Re:Search sabbatical program. Without the efforts of Re:Search, upwards of 80% of the collaborations in the consortium would not otherwise have come to fruition [140]. In this respect, Re:Search has achieved great success, getting a number of companies to donate patents, data, and know-how and facilitating forty-six license agreements and five collaborations aimed at technology transfer and capacity building in LMICs.

Re:Search currently relies on the goodwill of pharmaceutical companies and other patent holders for participation, and Providers often receive few benefits beyond reputational and humanitarian benefits. While a number of pharmaceutical companies have been eager to engage with Re:Search, this depends a lot on the leadership within an organization and their commitment to ND R&D. Fortunately, it seems that momentum has been building for addressing the ND problem in LMICs.

With respect to the ability of Re:Search to speed up the development of new medicines, vaccines, and diagnostics for NTD, TB, and malaria, it is hard to say what its impact has been to date. These sorts of developments takes years to move from early-stage R&D to a final product, and thus it will be a number of years before it any tangible product born out of Re:Search materializes. However, by providing a meeting place for diverse organizations from around the world and foster collaborations between these groups of people, Re:Search certainly has laid the groundwork for achieving this goal.

## 12. Conclusion

In order to assess the value of patent pools for global health, more time is necessary to assess whether the two pools—the MPP and Re:Search—are accomplishing their stated objectives and offering sufficient benefits over existing alternatives that aim to facilitate access to essential medicines.

While the MPP, to date, has received better licensing terms than existing voluntary licenses, it will take a few years before any new FDCs or pediatric formulations are developed more efficiently and cheaply from the licenses in the MPP. There seems to be interest on the part of sub-licensees to develop these formulations, with many licensees expressing an intention to start the process, but to date, none have actually began the process. However, momentum is building among pharmaceutical companies with respect to negotiating licenses with the MPP, as pharmaceutical companies seem to be increasingly willing to work with the MPP to reduce the price of ARVs in the long-term. Thus, the MPP can be said to be going beyond the status quo with respect to increasing access to ARVs, both through negotiating better licensing terms with pharmaceutical companies than current voluntary licenses offer and increasing the access initiatives of pharmaceutical companies and have thus far not engaged with the MPP.

The value of Re:Search, an upstream patent pool for previously neglected diseases, will take even more time for success to be realized. It seems that there is a lot

of interest on the part of pharmaceutical companies, smaller biotechnology companies, PDPs, universities, and other research institution to work with Re:Search to increase access to IP and know-how related to neglected diseases. However, because Re:search is trying to foster the development of novel drugs and a lot of ND treatments are still in the very early stages of drug discovery, it will take a number of years—maybe even a decade or more—for the full benefits of Re:Search to be realized. However, Re:Search has proven successful in fostering collaborations between entities that would otherwise not occur, and these collaborations may eventually spur new, better treatments for neglected diseases that would otherwise not come to fruition.

## Appendix A: Voluntary Licenses

Originator Company	Drug	Licensees	Geographic Scope (# of countries)	Publicly Available Info
ViiV	MVC	0	none	
ViiV	ABC	1 (Aspen)	SSA + LDCs + LICs (69)	No
ViiV	3TC	8 (Aspen; Cipla Medpro; Feza; Thembalami; Biotech Laboratories; Sonke; Cosmos)	SSA + LDCs + LICs (69)	
ViiV	DLG	0	None	
BMS	ATV	7 (Aspen, Mylan, Emcure, 3 others unknown; tech transfer agreement with Brazil for manufacture by Farmanguinhos)	SSA + India (48)	Royalty-free
BMS	ddI	11 (Adcock-Ingram; Aspen; Danpong-Adams; Enaleni; Sonke; Varichem; Thembalani; AfrikaBiopharm; Aurobindo; Emcure; Ranbaxy, Mylan (Matrix))	SSA + India (49)	Immunity from suit allowing for production of ddI + d4T; royalty-free
BMS	d4T		SSA + India (49)	
J&J	ETV	2 (Aspen; Emcure)	SSA + LDCs (48)	Royalty-free
J&J	DRV	2 (Aspen,	SSA + LDCs +	Royalty-free



		Emcure)	India (66)	
J&J	RIL	5 (Aspen; Emcure; Hetero; Mylan (Matrix); Strides)	112 country list	Royalty-bearing
Roche	SQV	12 (Adcock Ingram; Addis; Aspen; Beximco; CAPS; Cosmos; Muhimbili University; Radiant; Regal; Shelys; Universal Corporation; Varichem; Zenufa)	SSA + LDCs (65)	
Abbott	LPV/r, r	0	none	
Merck	RAL	2 (Emcure, Mylan)	SSA + LICs (60)	
Merck	EFV	7 (Emcure; Arrow; Sonke; Aspen; Aurobindo; Cipla-Medpro; Adcock Ingram)	South Africa (1) [no patents filed for EFV in the rest of SSA]	Royalty-free
Boehringer	NVP	10 (Cosmos; Universal Pharmacy; Aspen; Gemini; Memphis; Cipla Medpro; Kimia Farma; Adcock Ingram/Ranbaxy (Thembalami))	All Africa + LDCs + LICs (78)	Also has non-asserts with 7 generic companies( Cosmos; Aspen; Biotech Laboratories; Memphis; Aurobindo; Cipla; Emcure; Strides)

Gilead (in addition to MPP license)	COBI	4	For exclusive supply in specific countries	10-15% royalty on supply under additional agreements
-------------------------------------	------	---	--	--

Source: "Barriers to Accessing Generics: The Restrictions Posed by Certain Voluntary License Agreements," Medecins Sans Frontieres Access Campaign, accessed February 23, 2014, <http://utw.msfaaccess.org/annexes/4fe7877930d7010002000003>

## Appendix B: Countries Eligible for Pharmaceutical Company Price Discounts

Pharmaceutical Company	Eligible Countries
AbbVie (Abbott)	<p><b>Category 1 Countries:</b> All African countries and all LDCs outside of Africa</p> <p><b>Category 2 Countries:</b>  Albania, Armenia, Azerbaijan, Belarus, Bolivia, Bosnia and Herzegovina, China, Colombia, Dominican Republic, Ecuador, El Salvador, Fiji, Georgia, Guatemala, Guyana, Honduras, India, Indonesia, Jamaica, Jordan, Kazakhstan, Kyrgyzstan, Macedonia, Marshall Islands, Micronesia, Moldova, Mongolia, Montenegro, Nicaragua, Pakistan, Papua New Guinea, Paraguay, Peru, Philippines, Serbia, Sri Lanka, Suriname, Syria, Tajikistan, Thailand, Tonga, Turkmenistan, Ukraine, Uzbekistan, Vietnam</p>
Boehringer Ingelheim	<p><b>Category 1 Countries:</b> all LDCs; all low-income countries; all of Africa</p> <p><b>Category 2 Countries:</b> all middle-income countries not covered in Category 1</p>

BMS

**Category 1 Countries:** all of Sub-Saharan Africa (except Southern African countries); low-income countries (except Korea, Kyrgyzstan, Moldova and Uzbekistan)

**Category 2 Countries:** Southern African countries (Botswana, Lesotho, South Africa, Malawi, Mozambique, Swaziland, Zambia, and Zimbabwe)

**All Other Developing Countries:** prices in this category negotiated on a case-by-case basis

Gilead

**Category 1 Countries:** 111 countries, including all African countries and additional countries based on a country's economic status and HIV prevalence

**Category 2 Countries:** 24 countries, based on a country's economic status and HIV prevalence

Janssen (Johnson & Johnson)

**Category 1 Countries:** all Sub-Saharan African countries and all LDCs outside of Africa

**All Other Low- and Middle-Income Countries:** prices negotiated on a case-by-case basis

Merck (Efavirenz and Raltegravir)

**Category 1 Countries:** All countries in Sub-Saharan Africa and low-income countries

**Lower-Middle and Upper-Middle Income Countries:** prices discounted from *high-income* country prices, negotiated on a case-by-case basis, based on country income and disease burden

Merck (TDF/FTC/EFV)

**Category 1 Countries:**  
Afghanistan, Angola, Antigua and Barbuda, Bangladesh, Belize, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Congo (DRC), Côte d'Ivoire, Djibouti, Dominica, Dominican Republic, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Grenada, Guatemala, Guinea-Bissau, Guinea, Guyana, Haiti, Honduras, Jamaica, Kenya, Kiribati, Laos, Lesotho, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Moldova, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Pakistan, Panama, Papua New Guinea, Rwanda, São Tomé and Príncipe, Senegal, Sierra

ViiV Healthcare

Leone, Solomon Islands,  
Somalia, South Africa, St Kitts  
and Nevis, St Lucia, St Vincent  
and the Grenadines, Samoa,  
Sudan, Suriname, Swaziland,  
Tanzania, Timor-Leste, Togo,  
Trinidad and Tobago, Tuvalu,  
Uganda, Ukraine, Vanuatu,  
Yemen, Zambia, Zimbabwe

**Category 2 Countries:** Bolivia,  
Indonesia, Kyrgyzstan,  
Mauritius, Mongolia,  
Nicaragua, Seychelles, Syria,  
Tajikistan, Uzbekistan,  
Vietnam

**Category 1 Countries:** all low-  
income countries, all LDCs,  
and all Sub-Saharan African  
countries

---

*Source: Medecins Sans Frontieres Access Campaign. 2013. Untangling the Web of Antiretroviral Price Reductions, 16<sup>th</sup> Edition.*

## Appendix C: Comparison of MPP Licenses

License Term	Gilead License	ViiV License (ABC)	BMS License	ViiV License (DTG for Adult and Pediatric Use; ABC for adult use)
Drugs Covered	TDF, FTC, EVG, COBI, "QUAD"	ABC (pediatric formulation)	ATV	DTG and ABC for adult use; DTG for pediatric use
Geographic Scope	TDF and FTC territories: 121 countries COBI territory: 102 countries EVG and Quad: 99 countries	118 LMICs	110 LMICs	<b>Adult:</b> 66 royalty-free countries; 6 royalty countries <b>Pediatric:</b> 121 LMICs
Excluded Middle-Income Countries	<b>MICs excluded from TDF territory:</b> Albania, Egypt, Iraq, Marshall Islands, Micronesia, Morocco, Paraguay, The Philippines, Ukraine, West Bank and Gaza, Algeria, American Samoa, Argentina, Azerbaijan, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Iran, Jordan, Latvia, Lebanon, Libya, Lithuania, Macedonia, Malaysia, Mexico, Montenegro, Panama, Peru, Romania, Russia, Serbia, Tunisia, Turkey, Uruguay, and Venezuela;	Albania, Timor-Leste, Ukraine, American Samoa, Antigua & Barbuda, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, China, Dominica, Grenada, Jordan, Kazakhstan, Latvia, Lithuania, Macedonia, Mexico, Montenegro, Peru, Romania, Russia, Serbia, Suriname, Turkey, Uruguay, Venezuela	Albania, Egypt, Indonesia, Morocco, Paraguay, The Philippines, Ukraine, Vietnam, Algeria, American Samoa, Argentina, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Iran, Jordan, Latvia, Lebanon, Lithuania, Macedonia, Malaysia, Mexico, Montenegro, Peru, Romania, Russia, Serbia, Thailand, Tunisia, Turkey, Uruguay, Venezuela	<b>Adult:</b> Albania, Algeria, American Samoa, Antigua & Barbuda, Argentina, Armenia, Azerbaijan, Belarus, Belize, Bolivia, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Fiji, Georgia, Granada, Guatemala, Guyana, Honduras, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Latvia, Lebanon, Libya, Lithuania, Macedonia, Malaysia, Maldives, Marshall Islands, Mexico, Micronesia, Moldova, Mongolia, Montenegro,

	<p><b>MIC excluded from COBI territory:</b> TDF excluded MICs; El Salvador, Indonesia, Sri Lanka, Turkmenistan, Thailand, Namibia, Kazakhstan, Ecuador, Botswana, and Costa Rica</p> <p><b>MICs excluded from EVG/QUAD territory:</b> TDF excluded MICs; COBI excluded MICs; Dominican Republic</p>			<p>Morocco, Nicaragua, Pakistan, Palau, Panama, Papua New Guinea, Paraguay, Peru, Romania, Russia, Serbia, Sri Lanka, St. Lucia, St. Vincent, Suriname, Syria, Thailand, Timor-Leste, Tonga, Tunisia, Turkey, Ukraine, Uruguay, Uzbekistan, Venezuela, West Bank &amp; Gaza</p> <p><b>Pediatric:</b> Albania, Timor-Leste, American Samoa, Antigua &amp; Barbuda, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, China, Dominica, Granada, Jordan, Kazakhstan, Latvia, Lithuania, Macedonia, Mexico, Montenegro, Romania, Russia, Serbia, St. Lucia, St. Vincent, Suriname, Turkey, Uruguay</p>
Royalties	<p>3% for TDF and TDF combinations; 5% for EVG and EVG combinations; 5% for COBI and COBI combinations; waived for pediatric formulations; waived for FTC</p>	Royalty-free	<p>3% in countries BMS has a patent <i>granted and in force</i>; royalties go back to community-based HIV organizations in country in which royalty was charged; royalties waived for pediatric</p>	<p><b>Adult:</b> Royalty-free 66 LMICs; sliding scale royalty scheme based on country per-capita income in 6 MICs (Tier 1 (5%): India, Vietnam, The Philippines; Tier 2 (7.5%): Indonesia, Egypt; Tier 3 (10%): Turkmenistan)</p> <p><b>Pediatric:</b> royalty-free</p>



Field of Use	TDF: HIV and Hepatitis B; COBI and EVG: “any use that is consistent with the label approved by the FDA or applicable foreign regulatory authority”	Treatment of pediatric HIV	formulations Treatment of HIV	<b>Adult:</b> treatment of adult HIV <b>Pediatric:</b> treatment of pediatric HIV
Grant-Back Provision	Improvements flow back to Gilead only	Improvements flow back to ViiV and the MPP	Improvements flow back to BMS and the MPP	<b>Adult and Pediatric:</b> improvements flow back to ViiV and the MPP
Treatment of Formulation of Combination Products	No restrictions on formulation of combinations for TDF and COBI; for combinations with EVG, sub-licensee must obtain consent from Gilead prior to sale of combination	No restrictions on formulation of combinations	No restrictions on formulation of combinations	<b>Adult:</b> no restrictions on formulation of combinations
Technology Transfer Package	Yes	No	Yes; but if licensee uses technology transfer package, cannot supply ATV outside the covered territory	<b>Adult and Pediatric:</b> No
Waiver of Data Exclusivity	Yes	Yes	Yes	<b>Adult and Pediatric:</b> Yes
MPP Right to Enforce Agreement	No	Yes	Yes	Yes
Eligible Sub-Licensees	Only Indian generic manufacturers	Any generic manufacturer anywhere in the world	Any generic manufacturer anywhere in the world	<b>Adult and Pediatric:</b> any generic manufacturer,

Sourcing and supplying APIs	Only from/to Gilead or another sub-licensee	No restrictions within license territory	No restrictions within license territory	<p>anywhere in the world</p> <p><b>Adult:</b> no restrictions within royalty-free license territory; limited to supply for sale in public market only in royalty countries</p> <p><b>Pediatric:</b> no restrictions within license territory</p>
Ability to Supply Outside License Territory	Sub-licensees can supply outside covered territory if drug is off-patent or country issues a compulsory license	Sub-licensees can supply outside covered territory if ABC is off-patent or a country issues a compulsory license	Sub-licensees can supply outside covered territory if ATV is off-patent or a country issues a compulsory license	<p><b>Adult and Pediatric:</b> sub-licensee can supply outside covered territory if DTG (or ABC) is off-patent or a country issues a compulsory license</p>

## Appendix D: Comparison of MPP-Gilead License to 2006 Gilead Voluntary Licenses for TDF

License Term	MPP-Gilead License	2006 Gilead Voluntary Licenses
Geographic Scope	112 countries (but, if TDF portion of license is terminated, sub-licensees can supply TDF to 143 countries where no TDF patent is in force)	95 countries
Restrictions on Sale Outside License Territory	Sale outside license territory permitted in countries where TDF is off-patent	No sale permitted outside license territory, regardless of patent status of TDF
Termination of License	Unbundling clause that permits sub-licensees to terminate the TDF portion of the license at any time, for any reason	Licensees not permitted to terminate license
Payment of Royalties	3% royalty	5% royalty
Field of Use	HIV and Hepatitis B	HIV only
Treatment of Compulsory Licensing	Sub-licensees can supply licensed drugs to excluded countries if they have issued a compulsory license	No public knowledge whether or not this license contained a similar provision
API Restrictions	Sub-licensees can only purchase APIs from and supply APIs to Gilead or another sub-licensee	Sub-licensees can only purchase APIs from and supply APIs to Gilead or another sub-licensee

## Appendix E: Private Sector ND R&D Facilities

Company	R&D center	Location	Disease	Since
<b>AstraZeneca</b>	Bangalore Research Institute	Bangalore, India	Tuberculosis Malaria	2003 2009
<b>GlaxoSmithKline</b>	Tres Cantos Medicines Development Campus	Tres Cantos, Spain	Malaria Tuberculosis Kinetoplastids	2002
<b>MSD/Merck &amp; Co.</b>	MSD Wellcome Trust Hilleman Laboratories	New Delhi, India	Rotavirus	2009
<b>Novartis</b>	Novartis Institute for Tropical Diseases (NITD)	Singapore	Dengue fever Malaria Tuberculosis	2002
<b>Novartis</b>	Novartis Vaccines Institute for Global Health (NVGH)	Siena, Italy	Diarrheal diseases Salmonella	2008
<b>Novartis</b>	Genomics Institute of the Novartis Research Foundation (GNF)	La Jolla, USA	Chagas disease Leishmaniasis Malaria	2010
<b>Novartis</b>	Novartis Institutes for Biomedical Research (NIBR)	Horsham, UK	Infectious diarrhea	2009

Source: "2012 Status Report on Pharmaceutical R&D to Address Diseases that Disproportionately Affect People in Low- and Middle-Income Countries." IFPMA, 2012.

## Appendix F: Re:Search Collaboration Agreements

Collaboration Participants	Collaboration Description	Collaboration Overview
Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR) and Stanford University	Develop and test a diagnostic for helminthes	Collaboration will enable the sharing of stool samples to support Stanford's helminth diagnostic product development and testing
GSK and Center for World Health and Medicine (CWHM)	MetAp-1 inhibitor drug development for TB	GSK has shared information and data with CWHM and has provided insights into the development of MetAp-1 inhibitors for TB; information sharing resulted in approximate savings of \$50,000 and 3 months of FTE time for CWHM
AstraZeneca (AZ) and iThemba Pharmaceuticals	Computational chemistry support for TB drug candidates	AZ is providing computational and predictive chemistry know-how and support to iThemba in order to improve compound characteristics for TB drug candidates.
AZ and University of California at San Francisco (UCSF)	Cysteine protease inhibitors library for multiple ND drug discovery	AZ is providing UCSF with a diverse cysteine protease inhibitor compound library to screen against <i>T. cruzi</i> , <i>T. brucei</i> , <i>P. falciparum</i> and <i>S. mansoni</i> . Agreement was amended to include screening of compounds against hookworm
AZ and University of Dundee	Glycogen Synthase Kinase 3 (GSK-3) inhibitors for kinetoplastids drug discovery	AZ is providing a GSK-3 inhibitor compound library to Dundee to screen against Kinetoplastids.
NIH and Emory University	In-kind support from the NIH for dengue drug discovery	This agreement provides Emory University researcher with biology expertise and support from the NIH for RNA-dependent RNA polymerase inhibitor program for dengue. The characterization of the compounds included screening against the Rift Valley Fever virus.

GlaxoSmithKline (GSK) and University of Washington (UW)	Characterize pre-clinical compounds for malaria	This agreement enables the sharing of confidential information and transfer of UW compounds to GSK. Compounds will be re-profiled at GSK in Tres Cantos for transmission blocking in malaria.
AstraZeneca (AZ) and Anacor	Fabl inhibitor compound structures and data sharing for Shigella	AZ has shared knowledge and data on FabI inhibitors and compound structures to inform and support Anacor's development of products for Shigella.
Merck and University of California at San Francisco (UCSF)	Compounds for Schistosomiasis	Confidentiality agreement enabled discussions around compound selection. Collaborative study agreement allows for the sharing of compounds with UCSF for screening against <i>S. mansoni</i> .
GlaxoSmithKline (GSK) and University of Washington (UW)	Research collaboration around multi-kinase inhibitors in malaria	GSK to work collaboratively with UW to identify lead compound in a series. The initial compounds screened at UW were from the Tres Cantos Anti-Malaria (TCAMS) data set.
PATH and Kumasi Center for Collaborative Research in Tropical Medicine (KCCR)	Co-development of Onchocerciasis diagnostic	Confidentiality agreement will enable discussions and planning for co-development of a novel Onchocerciasis diagnostic.
AstraZeneca (AZ) and Anacor	Research collaboration around tuberculosis drug discovery	Anacor compounds will be screened against AZ tuberculosis targets.
AstraZeneca (AZ) and Liverpool School of Tropical Medicine	Sharing of preclinical compound libraries for malaria	This agreement will enable sharing of AZ's advanced preclinical and clinical compounds for screening against the malaria parasite.
AstraZeneca (AZ) and University of California San Francisco (UCSF)	Sharing of CYP51 inhibitors for screening against kinetoplastids	Non-azole CYP51 inhibitors and a diverse set of compounds from AZ will be made available to UCSF for screening against Chagas and Leishmaniasis.
AstraZeneca (AZ) and McGill University	Testing of anti-helminthic compounds in drug-resistant mutants	AZ compounds that were promising in a DNDi phenotypic anti-helminth screen will be tested at McGill University against <i>C. elegans</i> mutant strains to elucidate the mechanism of action.

Infectious Disease Research Institute (IDRI ) and South African Medical Research Council (MRC))	Expertise and advise will be shared to optimize natural product derived compounds	IDRI will share expertise and provide advice to improve solubility and bioavailability of anti-TB compounds developed at MRC /University of Cape Town.
Eisai and University of Dundee	Sharing of calcium channel blocker compound	Eisai has transferred a compound to the University of Dundee under an MTA for testing against the malarial parasite.
Eisai and University of Dundee	Sharing of proteasome inhibitor compound	Eisai has transferred a compound to the University of Dundee under an MTA for testing against the malarial parasite.
Pfizer and Center for World Health and Medicine (CWHM)	Sharing of compounds to support anti-diarrheal product development	Pfizer will provide two compounds to CWHM for evaluation in a rat diarrhea model.
AstraZeneca (AZ) and Stanford University	Advice and knowledge sharing for peptide formulation	AZ (MedImmune) will share technical know-how with Stanford researcher to enable peptide formulation for cutaneous leishmaniasis.
Eisai and University of Kansas (KU)	Advice and knowledge sharing for anti-fungal formulation	One-way CDA enabled sharing of expertise and ideas to address formulation issues. KU faculty member confirmed that all strategies had been comprehensively explored by Eisai.
Novartis and McMaster University	Sharing of reagent for dengue research	Novartis shared a polyclonal anti-dengue antibody with a McMaster University researcher.
AstraZeneca (AZ) and Northeastern University	Computational Support for compounds against Human African Trypanosomiasis (HAT)	AZ will provide computational prediction of blood brain barrier penetration for a set of compounds from Northeastern University.
Sanofi & Center for World Health & Medicine (CWHM)	Testing of neutral endopeptidase inhibitors for use against acute secretory diarrhea (ASD)	Sanofi has granted access to its neutral endopeptidase inhibitors for evaluation in CWHM's animal model.
AstraZeneca (AZ) and Anacor	Fabl inhibitor compound structures and data sharing for Shigella	AZ has shared knowledge and data on FabI inhibitors and compound structures to inform and support Anacor's development of products for

AstraZeneca (AZ) and Swiss Tropical and Public Health Institute (Swiss TPH)	Sharing of inhibitors of <i>M. tuberculosis</i> for screening against Buruli ulcer	Shigella. AZ will provide compounds including their compound in clinical trials against TB for screening against <i>M. ulcerans</i> , the causative agent for Buruli ulcer.
Merck and Emory University	Sharing of protein purification know how	Merck will share know how for membrane bound protein purification with a researcher working on tuberculosis at Emory.
AZ and Liverpool STM	Access to compounds for Onchocerciasis and lymphatic filariasis treatment	AZ is providing Liverpool STM scientists with access to its labs and high-throughput screens of compounds to test against <i>Wolbachia</i> in order to identify new Onchocerciasis and lymphatic filariasis therapies.
Eisai and Northeastern	A discussion between Northeastern and Eisai to obtain advice from Eisai on SARs for the design of phosphodiesterase inhibitors of HAT.	A discussion between Northeastern and Eisai to obtain advice from Eisai on SARs for the design of phosphodiesterase inhibitors of HAT.
AstraZeneca (AZ) and Eskitis	Natural products for tuberculosis	Eskitis will share its natural product library with AZ Bangalore to screen against tuberculosis.
AstraZeneca (AZ) and McGill	Compound libraries for anti-helminthic HTS	AZ will provide McGill with ~10,000 diverse compounds to test against <i>C. elegans</i> . Data from the screen will be included in a re-submission of a Wellcome Trust grant application.
Eisai and Infectious Disease Research Institute (IDRI)	Eisai provided IDRI with advice regarding parameters to consider during vaccine adjuvant design.	Eisai provided IDRI with advice regarding parameters to consider during vaccine adjuvant design.
GlaxoSmithKlein (GSK) and National Institute of Immunology, India (NII)	Kinase inhibitors for malaria	GSK will share kinase inhibitors with NII to use to study various molecular pathways in malaria.
Kumasi Centre for	MOU to explore several	An MOU was signed between KCCR



Collaborative Research, Ghana (KCCR) and Northeastern University	collaboration opportunities	and Northeastern that will enable the institutions to explore grant opportunities together, develop exchange between students, and conduct collaborative lab projects together.
National Institute of Health (NIH) and Infectious Disease Research Institute (IDRI)	Natural products for tuberculosis	NIH will provide IDRI with natural product compounds to screen against tuberculosis.
Pfizer and 60 Degrees Pharmaceuticals (60P)	Sharing investigators brochure	Pfizer will provide its investigators brochure for a discontinued compound to 60P. 60P is hoping to repurpose the drug as a dengue treatment.
Pfizer and McGill	Anti-inflammatory compounds for malaria	Pfizer will share JAK inhibitors with McGill to screen in a cerebral malaria model.
Merck and University of California, San Francisco (UCSF)	Providing HMG Co-A reductase inhibitors for schistosome research	Merck will share compounds with UCSF to screen against Schistosomiasis
AZ and Liverpool STM	Sharing set of compounds for malaria	AZ will share an additional set of compounds with Liverpool STM to screen against malaria.
GSK and NII	Kinase inhibitors for tuberculosis	GSK will share kinase inhibitors with NII to study tuberculosis metabolic pathways.
GSK and UCSF	Kinase inhibitors for Schistosomiasis	GSK will share a set of kinase inhibitors with UCSF to test against Schistosomiasis.
GSK and UCSF	Kinase inhibitors for Schistosomiasis	GSK will share a second set of kinase inhibitors with UCSF to test against Schistosomiasis.
Pfizer and PATH	Pfizer will share an investigator brochure with PATH. PATH aims to repurpose a drug to treat diarrheal diseases.	Pfizer will share an investigator brochure with PATH. PATH aims to repurpose a drug to treat diarrheal diseases.
Sanofi and CWHM	Sharing compounds to	Sanofi provided two compounds to

	support anti-diarrheal product development	CWHM to evaluate in a rat diarrhea model.
U. of Lagos and Stanford	Testing paper microscope for malaria	The University of Lagos will host two researchers from Stanford to test their paper microscope using field samples.
Kitis Institute, Griffith University and Swiss Tropical and Public Health Institute (Swiss TPH)	Natural products to screen against soil-transmitted helminths and schistosome.	

## References

1. "Fixed Dose Combinations (FDCs)," World Health Organization, accessed March 18, 2014, [http://apps.who.int/prequal/info\\_applicants/Guidelines/info\\_for\\_applicants\\_guidelines\\_fdcs.htm](http://apps.who.int/prequal/info_applicants/Guidelines/info_for_applicants_guidelines_fdcs.htm).
2. Medecins Sans Frontieres Access Campaign. 2013. *Untangling the Web of Antiretroviral Price Reductions*, 16<sup>th</sup> Edition.
3. "HIV/AIDS Fact Sheet," World Health Organization, last modified October 2013, accessed February 22, 2014, <http://www.who.int/mediacentre/factsheets/fs360/en/>.
4. Michelle Childs, "Towards a Patent Pool for HIV Medicines: The Background," *The Open AIDS Journal* 4, (2010).
5. "10 Facts on HIV/AIDS," World Health Organization, last modified November 2013, accessed February 22, 2014, <http://www.who.int/features/factfiles/hiv/en/>.
6. UNAIDS. November 2013. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013*. UNAIDS/JC2502/1/E.
7. World Health Organization. June 2013. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*.
8. Anthony D. So and Quentin Ruiz-Esparza, "Technology Innovation for Infectious Diseases in the Developing World," *Infectious Diseases of Poverty* 1, no. 2 (2012).
9. World Health Organization. 2010. *Working to Overcome the Global Impact of Neglected Tropical Diseases*. WHO/HTM/NTD/2010.1.
10. Roderik F. Viergever, Robert F. Terry, and Ghassan Karam, "Use of Data from Registered Clinical Trials to Identify Gaps in Health Research and Development," *Bulletin of the World Health Organization* 91, no. 6 (2013).

11. Tim K. Mackey and Bryan A. Liang, "Global Health Policy Coordination to Address Neglected Tropical Diseases," *Tropical Medicine and International Health* 17, no. 9 (2012).
12. Results for Development Institute, Center for Global Health R&D Policy, Rebecca Goulding and Amrita Palriwala. 2012. *Patent Pools: Assessing their Value-Added for Global Health Innovation and Access*.
13. "Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)," 1869 U.N.T.S. 299 (Marrakesh Agreement Establishing the World Trade Organization, April 5, 1994).
14. John Braithwaite and Peter Drahos, "Intellectual Property, Corporate Strategy, Globalisation: TRIPS in Context," *Wisconsin International Law Journal* 20, no. 3 (2002).
15. World Intellectual Property Organization. 2007. *WIPO Patent Report: Statistics on Worldwide Patent Activities*.
16. George K. Foster, "Comment: Opposing Forces in a Revolution in International Patent Protection: The U.S. and India in the Uruguay Round and its Aftermath," *UCLA Journal of International Law & Foreign Affairs* 3 (1998).
17. James Love, "Four NGOs Ask NIH to Grant Open Licenses to Ritonavir Patents under Bayh-Dole March-in Provisions," *Knowledge Ecology International* (blog), October 25, 2012, accessed March 2, 2014, <http://keionline.org/node/1573>.
18. "Pharmaceutical Industry," World Health Organization, accessed February 1, 2014, <http://www.who.int/trade/glossary/story073/en/>.
19. Carolyn Deere, *The Implementation: The TRIPS Agreement and the Global Politics of Intellectual Property Reform in Developing Countries* (Oxford University Press, 2009).
20. United Nations Conference on Trade and Development. 2011. *Investment in Pharmaceutical Production in the Least Developed Countries: A Guide for Policymakers and Investment Promotion Agencies*. UNCTAD/DIAE/PCB/2011/5.
21. "Declaration on the TRIPS Agreement and Public Health," World Trade Organization, 2001.

22. "Responding to Least Developed Countries' Special Needs in Intellectual Property," World Trade Organization, October 16, 2013, accessed March 5, 2014, [http://www.wto.org/english/tratop\\_e/trips\\_e/ldc\\_e.htm](http://www.wto.org/english/tratop_e/trips_e/ldc_e.htm).
23. Reed Beall and Randall Kuhn, "Trends in Compulsory Licensing of Pharmaceuticals since the Doha Declaration: A Database Analysis," *PLoS Med* 9, no. 1 (2012).
24. Robert C. Bird, "Developing Nations and the Compulsory License: Maximizing Access to Essential Medicines While Minimizing Investment Side Effects," *Journal of Law, Medicine, & Ethics* 37, no. 2 (2009).
25. Amir Attaran, "Assessing and Answering Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health: The Case for Greater Flexibility and a Nonjusticiability Solution," *Emory International Law Review* 17 (2003).
26. "TRIPS, TRIPS Plus, and Doha," Medecins Sans Frontieres Access Campaign, last modified July 2011, accessed February 20, 2014, <http://www.msfacecess.org/content/trips-trips-plus-and-doha>.
27. Tahir Amin, "Searching for Transparency: Improving Patent Information to Increase Access to Medicines," *Bridges weekly* 14, no. 4 (December 2010): accessed February 24, 2014, <http://ictsd.org/i/news/bridges/98758/>.
28. Jorge Bermudez and Ellen 't Hoen, "The UNITAID Patent Pool Initiative: Bringing Patents Together for the Common Good," *The Open AIDS Journal* 4 (2010).
29. Brenda Waning, Ellen Diedrichsen, and Suerie Moon, "A Lineline to Treatment: The Role of Indian Generic Manufacturers in Supplying Antiretroviral Medicines to Developing Countries," *Journal of the International AIDS Society* 13, no. 35 (2010).
30. "MSF Review of the July 2011 Gilead Licenses to the Medicines Patent Pool," Medecine Sans Frontieres Access Campaign, last modified December 19, 2011, accessed February 25, 2014, <http://www.msfacecess.org/content/msf-review-july-2011-gilead-licences-medicines-patent-pool>.

31. Sanchayita Kar, "Open Innovation: An Answer for Neglected Diseases," *Future Medicinal Chemistry* 2, no. 9 (2010).
32. Kevin Outterson, "Access to Global Disease Innovation" (November 15, 2006).
33. Thomas J. Bollyky, "Better, Cheaper, Faster: Strategies for Sustainable Treatment Access for the World's Poorest," *Stanford Journal of Law, Science, & Policy* (2011).
34. David Zakus et al., "Achieving a Dream: Meeting Policy Goals Related to Improving Drug Access," *The Open AIDS Journal* 4, no. 25-27 (2010).
35. Aarthi Rao, "New Technologies for Neglected Diseases: Can Tax Credits Help Biotechnology Companies Advance Global Health?," *Journal of Commercial Biotechnology* 17 (2011).
36. Wen L. Kilama, "The 10/90 Gap in Sub-Saharan Africa: Resolving Inequities in Health Research," *Acta Tropica* 112, no. 1 (2009).
37. Oxfam International. 2008. *Ending the R&D Crisis in Public Health: Promoting Pro-Poor Medical Innovation*.
38. Michael Heller, "Where Are the Cures? How Patent Gridlock is Blocking the Development of Lifesaving Drugs," *Forbes*, July 24, 2008, accessed March 4, 2014, <http://www.forbes.com/forbes/2008/0811/030.html>.
39. The Global Alliance for TB Drug Development. 2007. *Pathway to Patients: Charting the Dynamics of the Global TB Drug Market*.
40. Francesca Holt, Stephen J. Gilam, and Jeremiah M. Ngondi, "Improving Access to Medicines for Neglected Tropical Diseases in Developing Countries: Lessons Learned from Three Emerging Economies," *PLoS Neglected Tropical Diseases* 6, no. 2 (2012).
41. John Lerner and Jean Tirole, "Efficient Patent Pools," *American Economic Review* 94, no. 3 (2004).
42. The Innovation Partnership, E. Richard Gold et al. 2007. *Preliminary Legal Review of Proposed Medicines Patent Pool*.

43. Indrani Barpujari, "Facilitating Access or Monopoly: Patent Pools at the Interface of Patent and Competition Regimes," *Journal of Intellectual Property Rights* 15 (2010).
44. Chris Edlin, "The Importance of Patent Sharing in Neglected Disease Drug Discovery," *Future Medicinal Chemistry* 3, no. 11 (2011).
45. Joel Lexchin, "One Step Forward, One Step Sideways?: Expanding Research Capacity for Neglected Diseases," *BMC International Health and Human Rights* 10, no. 20 (2010).
46. C. Park et al., "Understanding Voluntary Licensing: An Analysis of Current Practices and Key Provisions in Antiretroviral Voluntary Licenses" (presented at the 19<sup>th</sup> International AIDS Conference, Washington, DC, 2012).
47. "Barriers to Accessing Generics: The Restrictions Posed by Certain Voluntary License Agreements," Medecins Sans Frontieres Access Campaign, accessed February 23, 2014, <http://utw.msfacecess.org/annexes/4fe7877930d7010002000003>.
48. Randall Kuhn and Reed F. Beall, "The Time for Pharmaceutical Compulsory Licensing has Expired," *Nature Medicine* 18, no. 8 (2012).
49. G. Fordham, *A New Look at Thai AIDS: Perspectives from the Margin* (New York: Berghahn Books, 2005).
50. Inthira Yamabhai et al., "Government Use Licenses in Thailand: An Assessment of the Health and Economic Impacts," *Globalization and Health* 7, no. 28 (2011).
51. S. Chasombat et al., "National Expansion of Antiretroviral Treatment in Thailand, 2000-2007: Program Scale-up and Patient Outcomes," *Journal of Acquired Immune Deficiency Syndrome* 50, no. 5 (2009).
52. "MSF Welcomes Move to Overcome Patent on AIDS Drug in Thailand," Medecins Sans Frontieres Access Campaign, accessed February 28, 2014, <http://www.msfacecess.org/our-work/overcoming-barriers-access/article/389>.
53. The World Bank: International Bank for Reconstruction and Development, Ana Revenga et al. 2006. *The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand*. Health, Nutrition, and Population Series.

54. United Nations Conference on Trade and Development. 2011. Local Production of Pharmaceuticals and Related Technology Transfer in Developing Countries: A Series of Case Studies by the UNCTAD Secretariat. UNCTAD/DIAE/PCB/2011.
55. Program on Information Justice and Intellectual Property, Jennryn Wetzler and Mihir Mankad. 2008. *Timeline for Thailand's Compulsory Licenses*.
56. "NHSO Extends Drug Licensing: Move Ensures AIDS Medications Available," *Bangkok Post*, June 15, 2010, accessed February 28, 2014, <http://ww1.aegis.org/news/bp/2010/BP100602.html>.
57. Mongkol Na Songkhla, "Comment on CL by Thai CSOs," *IP-Health* (blog), October 2, 2010, accessed February 28, 2014, [http://lists.keionline.org/pipermail/ip-health\\_lists.keionline.org/2010-October/000311.html](http://lists.keionline.org/pipermail/ip-health_lists.keionline.org/2010-October/000311.html).
58. Paul Cawthorne et al., "Access to Drugs: The Case of Abbott in Thailand," *The Lancet: Infectious Diseases* 7 (2007).
59. USTR, "2006 Special 301 Report: Executive Summary," Knowledge Ecology International, accessed March 1, 2014, [http://www.keionline.org/sites/default/files/ustr\\_special301\\_2006.pdf](http://www.keionline.org/sites/default/files/ustr_special301_2006.pdf).
60. International Federation of Pharmaceutical Manufacturers & Associations. 2013. *Policy Position: Voluntary Licenses and Non-Assert Declarations*.
61. Brook K. Baker, "Johnson & Johnson Non-Assert Agreement on Darunavir: More Questions than Answers," *Health Gap* (blog), February 15, 2013, accessed February 26, 2014, <http://healthgap.org/blog/2013/1/4/johnson-and-johnson-non-assert-agreement-on-darunavir-more-questions-than-answers>.
62. Suerie Moon et al., "A Win-Win Solution?: A Critical Analysis of Tiered Pricing to Improve Access to Medicines in Developing Countries," *Globalization and Health* 7, no. 39 (2011).
63. Hannah Waters, "Cheap Drugs Pulled Despite Wealth Gap in Middle-Income Countries," *Nature Medicine* 17, no. 9 (2011).



64. Owain D. Williams, "Access to Medicines, Market Failure and Market Intervention: A Tale of Two Regimes," *Global Public Health: An International Journal for Research, Policy, and Practice* 7, no. sup2 (2012).
65. James Love, "An Essential Health Care Patent Pool" (presented at the 19<sup>th</sup> International AIDS Conference, Barcelona, Spain, 2002).
66. Asher Mullard, "Straight Talk with...Ellen 't Hoen," *Nature Medicine* 16 (2010). (J)
67. Philippe Douste-Blazy and Jorge Bermudez, "GSK: Please Extend Patent Pool to AIDS Drugs," *The Lancet* 373 (2009).
68. Fanella Corrick, Robert Watson, and Sanjay Budhdeo, "Should Patents for Antiretrovirals be Waived in the Developing World?: Annual Varsity Medical Debate – London, 21 January 2011," *Philosophy, Ethics, and Humanities in Medicine* 6, no. 13 (2011).
69. Nicole Zeigler, Oliver Gassman, and Sascha Friesike, "Why Do Firms Give Away Their Patents for Free?," *World Patent Information* (2013).
70. "Amended and Restated License Agreement between Gilead Sciences and the Medicines Patent Pool," The Medicines Patent Pool, November 2012, accessed March 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/Amended-and-Restated-License-Agreement-November-2012.pdf>.
71. "Amendments to Pool/Gilead Licenses, November 2011," The Medicines Patent Pool, November 14, 2011, accessed February 13, 2014, <http://www.medicinespatentpool.org/licensing/current-licences/amendments-to-poolgilead-licences-november-2011/>.
72. Tahir Amin, "ITPC Letter to the Medicines Patent Pool Foundation and UNITAID on the Processes, Principles of MPP and its First License Agreement with Gilead," *IP-Health* (blog), October 11, 2011, accessed February 12, 2014, [http://lists.keionline.org/pipermail/ip-health\\_lists.keionline.org/2011-October/001403.html](http://lists.keionline.org/pipermail/ip-health_lists.keionline.org/2011-October/001403.html).
73. *Manoj Hirasingsh Pardeshi v. Gilead Sciences, Inc., USA*, Competition Commission of India (2013).
74. Esteban Burrone, interview by author, February 24, 2014.

75. "Medicines patent Pool, ViiV Healthcare Collaborate to Treat Pediatric HIV," The Medicines Patent Pool, February 27, 2013, accessed February 13, 2014, <http://www.medicinespatentpool.org/medicines-patent-pool-viiv-healthcare-collaborate-to-treat-paediatric-hiv/>.
76. The Medicines Patent Pool. 2013. *Report of the Medicines Patent Pool Expert Advisory Group on the Proposed Pediatric Collaboration with ViiV Healthcare*.
77. "License Agreement between ViiV Healthcare an the Medicines Patent Pool," The Medicines Patent Pool, February 13, 2013, accessed March 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/Viiv-MPP-Licence-Agreement.pdf>.
78. "Memorandum of Understanding between the Medicines Patent Pool Foundation and ViiV Healthcare," The Medicines Patent Pool, February 13, 2013, accessed March 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/Viiv-MPP-MOU.pdf>.
79. "FDA Approves New Drug to Treat HIV Infection," U.S. Food and Drug Administration, last modified August 13, 2013, accessed March 2, 2014, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm364744.htm>.
80. "Roche Strikes Deal with Medicines Patent Pool on Medicines Access," The Pharma Letter, August 8, 2013, accessed March 1, 2014, <http://www.thepharmaletter.com/article/roche-strikes-deal-with-medicines-patent-pool-on-medicines-access>.
81. "Medicines Patent Pool and Roche Sign HIV Medicines Agreement: Focus on Preventing Blindness in People Living with HIV," The Medicines Patent Pool, August 5, 2013, accessed March 5, 2014, <http://www.medicinespatentpool.org/medicines-patent-pool-and-roche-sign-hiv-medicines-agreement-focus-on-preventing-blindness-in-people-living-with-hiv/>.
82. The Medicines Patent Pool. 2013. *Report of the Medicines Patent Pool Expert Advisory Group on the Proposed Collaboration with Roche*.
83. "Agreement between Roche and the Medicines Patent Pool," The Medicines Patent Pool, August 5, 2013, accessed March 1, 2014,

<http://www.medicinespatentpool.org/wp-content/uploads/MPP-Roche-Agreement-5-August-20133.pdf>.

84. "UNITAID Welcomes Bristol Myers Squibb Agreement with the Medicines Patent Pool," UNITAID, December 12, 2013, accessed March 5, 2014, <http://www.unitaid.eu/en/resources/press-centre/statements/1300-unitaid-welcomes-bristol-myers-squibb-s-agreement-with-the-medicines-patent-pool>.
85. "MPP and Bristol-Myers Squibb Sign Agreement to Further Expand Access to a Key HIV Medicine," The Medicines Patent Pool, December 12, 2013, accessed March 6, 2014, <http://www.medicinespatentpool.org/mpp-and-bristol-myers-squibb-sign-agreement-to-further-expand-access-to-a-key-hiv-medicine/>.
86. "License and Technology Transfer Agreement Between Bristol-Myers Squibb and the Medicines Patent Pool," The Medicines Patent Pool, December 11, 2013, accessed March 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/MPP-License-and-technology-transfer-agreement-Signed.pdf>.
87. Brook K. Baker, "Analysis of Territorial Access Issues in the MPP/BMS Atazanavir License," Info Justice, December 16, 2013, accessed March 1, 2014, <http://infojustice.org/wp-content/uploads/2013/12/baker12162013.pdf>.
88. Joel E. Gallant et al., "Cobicistat Versus Ritonavir as a Pharmacoenhancer of Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-Naïve HIV Type 1-Infected Patients: Week 48 Results," *Journal of Infectious Diseases* 208, no. 1 (2013).
89. Patrice Trouiller et al., "Drug Development for Neglected Diseases: A Deficient Market and Public-Health Policy Failure," *The Lancet* 359 (2002).
90. Monique F. Mrazek and Elias Mossialos, "Stimulating Pharmaceutical Research and Development for Neglected Diseases," *Health Policy* 64 (2003).
91. Roderik F. Viergever, "The Mismatch between the Health Research and Development (R&D) that is Needed and the R&D that is Undertaken: An Overview of the Problem, the Causes, and Solutions," *Global Health Action* 6 (2013).
92. Joshua Cohen, Maria Staroselsky Dibner, and Andrew Wilson, "Development of and Access to Products for Neglected Diseases," *PLoS One* 5, no. 5 (2010).

93. Suerie Moon, Jorge Bermudez, and Ellen 't Hoen, "Innovation and Access to Medicines for Neglected Populations: Could a Treaty Address a Broken Pharmaceutical R&D System?," *PLoS Med* 9, no. 5 (2012).
94. World Health Organization. 2009. *Mortality and Burden of Disease Estimates for WHO Member States in 2004*.
95. M. Moran et al., "The Role of Product Development Partnerships in Research and Development for Neglected Diseases," *International Health* 2 (2010).
96. Joseph A. DiMasi and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 28 (2007).
97. Results for Development Institute: Center for Global Health R&D and Policy Assessment, Hassan Masum and Rachelle Harris. 2011. *Open Source for Neglected Diseases: Magic Bullet or Mirage?*.
98. T.J. Tucker and M.W. Makgoba, "Public-Private Partnerships and Scientific Imperialism," *Science* 320, no. 5879 (2008).
99. Minna Allarakhia, "Open-Source Approaches for the Repurposing of Existing or Failed Candidate Drugs: Learning from and Applying the Lessons across Diseases," *Drug Design, Development and Therapy* 7 (2013).
100. Linsey McGoey, "The Philanthropic State: Market-State Hybrids in the Philanthrocapitalist Turn," *Third World Quarterly* 35, no. 1 (2014).
101. Results for Development Institute: Center for Global Health R&D Policy Assessment, Aarthi Rao. 2011. *R&D Tax Credits: A Tool to Advance Global Health Technologies?*.
102. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. 2008. *Guidance for Industry: Tropical Disease Priority Review Vouchers*.
103. Institute of Medicine, Global Health Interest Group, Peter Hotez et al. 2013. *Strengthening Mechanisms to Prioritize, Coordinate, Finance, and Execute R&D to Meet Health Needs in Developing Countries*.

104. Sara E. Crager and Matt Price, "Prizes and Parasites: Incentive Models for Addressing Chagas Disease," *Journal of Law, Medicine & Ethics* (2009).
105. Nigel Williams, "Patent Issues," *Current Biology* 19, no. 5 (2009).
106. Susan Dentzer, "Eliminating Neglected Diseases in Poor Countries: A Conversation with Andrew Witty," *Health Affairs* 28, no. 3 (2009).
107. Simon Frantz, "New Neglected Disease Research Scheme Pools IP and Expertise," *Nature Reviews: Drug Discovery* 11 (2012).
108. "Guiding Principles of WIPO Re:Search," World Intellectual Property Organization Re:Search Consortium, accessed March 4, 2014, [http://www.wipo.int/research/en/about/guiding\\_principles.html](http://www.wipo.int/research/en/about/guiding_principles.html).
109. "WIPO Re:Search," World Intellectual Property Organization Re:Search Consortium, accessed March 4, 2014, <http://www.wipo.int/research/en/>.
110. Rachel Marusak Hermann, "WIPO Re:Search Bridges Public, Private Sectors for Neglected Disease Research," *IP-Watch* (blog), October 27, 2011, accessed March 4, 2014, <http://www.ip-watch.org/2011/10/27/wipo-research-bridges-public-private-sectors-for-neglected-disease-research/>.
111. Julia Fraser, "We WIPO, Global Experts Share Experiences on Open Collaboration," *IP-Watch* (blog), January 29, 2014, accessed March 4, 2014, <http://www.ip-watch.org/2014/01/29/at-wipo-global-experts-share-experiences-on-open-collaboration/#more-33953>.
112. International Federation of Pharmaceutical Manufacturers & Associations. 2012. *Status Report on Pharmaceutical R&D to Address Diseases that Disproportionately Affect People in Low- and Middle-Income Countries*.
113. Peter B. Simpson and Melvin Reichman, "Opening the Lead Generation Toolbox," *Nature Reviews: Drug Discovery* 13 (2014).
114. "Collaboration Agreements," World Intellectual Property Organization Re:Search Consortium, accessed March 4, 2014, <http://www.wipo.int/research/en/collaboration.html>.
115. Jennifer Dent, "Partnership Hub Snapshot," World Intellectual Property Organization Re:Search Consortium, January 2014, accessed March 4, 2014,

<http://archive.constantcontact.com/fs193/1102950884221/archive/1116232422957.html>.

116. All-Party Parliamentary Group on AIDS. July 2009. *The Treatment Timebomb: Report of the Inquiry of the All-Party Parliamentary Group on AIDS into Long-Term Access to HIV Medicines in the Developing World*.
117. The World Health Organization, Ye Lu, Patricia Hernandez, Dele Abegunde, and Tessa Edejer. 2011. *The World Medicines Situation 2011: Medical Expenditures*.
118. Ashley J. Stevens et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines," *The New England Journal of Medicine* 365, no. 6 (2011).
119. Susan K. Sell, "TRIPS-Plus Free Trade Agreements and Access to Medicines," *Liverpool Law Review* 28 (2007).
120. "India Rejects Sham Patent Application for Lifesaving HIV Drug: Pharmaceuticals in India Now Free to Help HIV Patients Worldwide," Initiative for Medicines, Access & Knowledge, January 2, 2011, accessed March 25, 2014, <http://www.i-mak.org/storage/FINAL%20Press%20Release%201-1-2011.pdf>.
121. Brenda Waning et al., "The Global Pediatric Antiretroviral Market: Analyses of product Availability and Utilization Reveal Challenges for Development of Pediatric Formulations and HIV/AIDS Treatment in Children," *BMC Pediatrics* 10, no. 74 (2010).
122. "Patent Status of ARVs," The Medicines Patent Pool, accessed March 26, 2014, <http://www.medicinespatentpool.org/patent-data/patent-status-of-arvs/>.
123. The World Health Organization. 2010. *Working to Overcome the Global Impact of Neglected Tropical Diseases: First WHO Report on Neglected Tropical Diseases*. WHO/HTM/NTD/2010.1.
124. "FAQ About Neglected Diseases," National Center for Advancing Translational Sciences, accessed March 26, 2014, <http://www.ncats.nih.gov/about/faq/neglected/neglected-faq.html>.
125. Philippe J. Guerin et al., "Viseral Leishmaniasis: Current Status of Control, Diagnosis, and Treatment, and a Proposed Research and Development Agenda," *The Lancet: Infectious Diseases* 2 (2002).

126. "Oxfam Response to Pharmacia's Non-Exclusive Voluntary License for Delavirdine," Oxfam International, January 24, 2003, accessed March 28, 2014, <http://www.cptech.org/ip/health/aids/oxfam01242003.html>.
127. Tahir Amin, "Voluntary Licensing Practices in the Pharmaceutical Sector: An Acceptable Solution to Improving Access to Affordable Medicines?," I-MAK, February 8, 2007, accessed March 28, 2014, <http://www.i-mak.org/storage/Oxfam%20-%20Voluntary%20Licensing%20Research%20IMAK%20Website.pdf>.
128. Inthira Yamabhai et al., "Government Use Licenses in Thailand: An Assessment of the Health and Economic Impacts," *Globalization and Health* 7, no. 28 (2011).
129. Nathan Ford et al., "Sustaining Access to Antiretroviral Therapy in the Less-Developed World: Lessons from Brazil and Thailand," *AIDS* 21, supp. 4 (2007).
130. The Kaiser Family Foundation and UNAIDS. July 2012. *Financing the Response to AIDS in Low- and Middle-Income Countries: International Assistance from Donor Governments in 2011*.
131. Alain Guilloux and Suerie Moon, "Hidden Price Tags: Disease-Specific Drug Donations: Costs and Alternatives," MSF/DND Working Group, February 2001, accessed March 30, 2014, [http://www.deolhonaspatentes.org.br/media/file/publicacoes/hidden\\_price\\_tags.pdf](http://www.deolhonaspatentes.org.br/media/file/publicacoes/hidden_price_tags.pdf).
132. "Boehringer Ingelheim Policy Paper on HIV/AIDS," Boehringer Ingelheim, February 2011, accessed March 30, 2014, [http://www.boehringer-ingelheim.com/content/dam/internet/opu/com\\_EN/document/01\\_news/05\\_Media\\_Material/policy\\_paper\\_on\\_hiv\\_aids.pdf](http://www.boehringer-ingelheim.com/content/dam/internet/opu/com_EN/document/01_news/05_Media_Material/policy_paper_on_hiv_aids.pdf).
133. Brook K. Baker and Eva Ombaka, "The Danger of In-Kind Drug Donations to the Global Fund," *The Lancet* 373 (2009).
134. Jamie Love, interview by author, February 18, 2014.
135. "Medicines Patent Pool, ViiV Healthcare Sign License for the Most Recent HIV Medicine to have Received Regulatory Approval," The Medicines Patent Pool, April 1, 2014, accessed April 1, 2014, <http://www.medicinespatentpool.org/medicines-patent-pool-viiv-healthcare->

[sign-licence-for-the-most-recent-hiv-medicine-to-have-received-regulatory-approval/](#).

136. "Report of the Medicines Patent Pool Expert Advisory Group on the Proposed License Agreements with ViiV Healthcare for Dolutegravir," The Medicines Patent Pool, accessed April 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/ViiV-DTG-EAG-Report.pdf>.
137. "The Medicines Patent Pool-ViiV Healthcare Dolutegravir Pediatric License," The Medicines Patent Pool, March 31, 2014, accessed April 1, 2014, <http://www.medicinespatentpool.org/wp-content/uploads/MPP-ViiV-Dolutegravir-Paediatric-Licence-Agreement.pdf>
138. "The Medicines Patent Pool-ViiV Health Care Dolutegravir and Abacavir Adult License," The Medicines Patent Pool, March 31, 2014, accessed April 1, 2014, [http://www.medicinespatentpool.org/wp-content/uploads/MPPF-ViiV\\_Agreement\\_Adults\\_online.pdf](http://www.medicinespatentpool.org/wp-content/uploads/MPPF-ViiV_Agreement_Adults_online.pdf).
139. The World Health Organization. April 2012. *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*.
140. Jennifer Dent, interview by author, March 25, 2014.