# REPORT

# Evaluation of the Gilead Access Program

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## Executive Summary

Voluntary licensing (VL) is an innovative strategy intended to improve access to essential medicines globally. Gilead Sciences Inc. is a leader among global research-and-development-oriented pharmaceutical companies in issuing voluntary licenses for its medicines as a central component of its global access strategies. Indeed, thanks to VL of tenofovir disoproxil fumarate (TDF) by Gilead to several generics manufacturers, an estimated thirteen million patients in low- and middle-income countries (LMICs) have received the life-saving HIV medication.

VL is currently used in conjunction with other strategies that also contribute to improving access, including compulsory licensing for patented medicines, patent waivers and non-enforcement in least-developed countries, companies' medicines donation programs, and others. Evidence suggests that while all of these strategies have their uses, VL has resulted in the steepest increases in the availability of medicines to patients in need. The large scope of Gilead's Access Program is unique and the first of its kind; it contributed both direct access and to the creation of the Medicines Patent Pool (MPP), a global VL mechanism. Gilead has expanded its VL program to include other HIV therapies and Hepatitis C treatments.

This report presents factors that have accelerated or hindered the Gilead Access Program's uptake and impact. It is based on literature- and interview-based research conducted by the Boston University School of Public Health that addressed the Gilead Access Program for TDF, and included some comparisons with VL of sofosbuvir for Hepatitis C and the work of the MPP. The findings show that Gilead's VL program successfully expanded access to treatment when implemented 1) in specific contexts and 2) in concert with other strategies. This report highlights the importance of both conditions.

VL is not a "magic bullet" that solves the vast problem of access to medicines, but it is an important element of a comprehensive approach. In particular, VL is a critical component for the pharmaceutical industry. The results of VL are overwhelmingly positive for innovator companies and generics manufacturers alike, as well as for patients and their providers. Ample empirical evidence exists for this finding, and it was expressed by several individuals interviewed during the research conducted for this report. Generics manufacturers especially have embraced the opportunities afforded by Gilead's program for VL and additional opportunities created under the Medicines Patent Pool (MPP).

The report also highlights opportunities to further improve access programs using VL as the core strategy. Elements of VL that lie within the control of manufacturers are the selection of eligible territories, quality assurance (including sourcing of active pharmaceutical ingredients), in-country registration of originator products, and others. Regarding the first element, selection of eligible territories, one key question is: which countries/populations are eligible to receive medicines manufactured under voluntary licenses? In the case of the Gilead Access Program, the company offered VL opportunities in countries where it did not plan to sell its originator products but where there was a significant population affected and in need of treatment. This report finds that Ecuador, a country excluded from the Gilead Access Program's territories, has struggled to gain access to affordable TDF-containing products.

The second and third elements—quality assurance and registration—are highly interconnected and related to whether the originator company requires prequalification (PQ) from the World Health Organization (WHO), the US Food and Drug Administration (FDA) tentative approval or market authorization by another stringent regulatory authority (SRA). The report finds that requiring quality assurance plays an important role in fostering uptake of products under VL. Whether the voluntary

license restricts the source of the active pharmaceutical ingredient (API) used in the production of the medication is also relevant to the price of the final product. In the case of the TDF program, generics manufacturers were required to source the API from Gilead-approved sources, which reportedly limited the degree to which the companies were able to reduce the costs of production.

Finally, the report notes that registration is a key role for originator companies. In the absence of registration of the original medication, generics manufacturers in some cases found the burden of providing data on new medicines prohibitive to introducing a new product into a country.

An important theme that emerges from the report is that creating access to medicines while ensuring the sustainability of the pharmaceutical industry's business model requires an "ecosystem" approach—that is, using multiple interconnected strategies. VL, whether managed through the MPP or bilaterally, represent complementary strategies, each with its own advantages. Where the MPP serves as a middle manager, issuing standardized voluntary licenses to eligible generics manufacturers for HIV and HCV medicines with major public health impact, it allows for more organized and coordinated approaches to access. However, bilateral VL agreements may provide a speediest way to bring new medicines to wider markets in specific cases.

The report also shows that the impact of VL—whether through a bilateral or MPP license—depends on a variety of external factors, beginning with a guarantee of demand for any new medication. Demand has two elements: the size of the population in need of the medication, necessitating good data on the prevalence of the disease in question; and a guarantee of financing to pay for the medication required by the population. In the case of VL, the latter condition requires governments and donors alike to commit to purchasing medications manufactured by generics companies. These components of the context are outside the control of innovator companies, but are central areas for influence by the global access movement. Indeed, the existence of global stakeholders interested in access to treatment represents another important contextual factor. In the case of TDF, the involvement of people living with HIV, activists, WHO and donors committed to creating access to antiretrovirals all strongly contributed to the success of the VL program.

The evidence presented in this report includes three country case studies that highlight the importance of these contextual factors. The three countries profiled, Ecuador, Thailand and Zambia, each represent a different constellation of contextual factors, including the prevalence of HIV/AIDS, the health care and pharmaceutical markets, and the socioeconomic and political situation. They also had different relationships with global stakeholders, including advocates for access to medicine. These contextual factors resulted in significantly different outcomes of the VL effort. Zambia was an early and successful adopter of TDF as a first-line medicine for HIV; Thailand has also successfully introduced it and created access through local production as well as importation. Ecuador, which was not an initial VL target area, has been much slower to adopt use of TDF and access remains limited, especially for the purposes of pre-exposure prophylaxis (PrEP).

Ultimately, this report shows that Gilead's VL program has been most successful when the following conditions were met:

- High prevalence of disease so that demand for treatment was broadly recognized by both public health and political stakeholders
- Strong knowledge among health care professionals and patients about the specific medication and its potential uses
- Limited domestic production of pharmaceuticals so that importation of generically produced medication was already a standard approach

- Strong support from health care financiers, including both government and donor agencies
- Political will existed to smooth regulatory and bureaucratic requirements in the introduction of new medications

For Gilead, VL of TDF can be seen as the first iteration of a VL-for-access program. The company's sofosbuvir VL program was version 2.0. Both of these programs provide important lessons as Gilead considers future access efforts. Voluntary licenses offer significant successes and few losses to the company. But there are improvements that can be made, particularly regarding which countries should be eligible for products created under VLs and when it is appropriate to do direct bilateral licenses and when working through the MPP is more effective.

The findings in this report provide some insights, but also raise many more research questions for further investigation. These include, among others, the following: which countries should be made eligible for products created under VLs? When it is appropriate to do direct bilateral licenses and when is working through the MPP is more effective? How do changes in health financing affect which access strategies are most efficient and effective? What is the the optimal number of licenses to issue when rolling out a new product? What measures of outputs and health outcomes are appropriate for assessing access? Are there best practices in implementation of VL and can they be replicated? What aspects of a national context should require adaptation of VL programming? Which stakeholders are best suited to take on the various required roles to truly expand access to medicines? It is our hope that this report demonstrates that research efforts on such topics can be productively, transparently and collaboratively undertaken by academic, industry, governmental and civil society stakeholders.

# Contents

## Abbreviations and Acronyms

| | |
|---|---|
| AIDS | Acquired immune deficiency syndrome |
| API | Active pharmaceutical ingredient |
| ARV | Anti-retroviral |
| ACTD | Association of Southeast Asian Nations (ASEAN) Common Technical Dossier |
| CL | Compulsory licensing |
| CPG | Clinical Practice Guideline |
| DTG | Dolutegravir |
| FDA | Food and Drug Administration |
| FDC | Fixed-dose combination |
| FTC | Emtricitabine |
| GAP | Gilead Access Program |
| GCP | Good clinical practices |
| GDP | Gross domestic product |
| GMP | Good manufacturing practices |
| GPO | Government Pharmaceutical Organization |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IP | Intellectual property |
| LDC | Least Developed Country |
| LMIC | Low- and middle-income country |
| MOH | Ministry of Health |
| MPP | Medicines Patent Pool |
| MSF | Médecins sans Frontières/Doctors Without Borders |
| MSP | Ministerio de Salud Pública |
| NGO | Non-governmental organization |
| PAHO | Pan-American Health Organization |
| PEPFAR | US President's Emergency Plan for AIDS Relief |
| PLHIV | Person/people living with HIV |
| PQ | Prequalification |
| PREP | Pre-Exposure Prophylaxis |
| SRA | Stringent regulatory authority |
| STG | Standard Treatment Guidelines |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |
| TRIPS | Agreement on Trade-Related Aspects of Intellectual Property Rights |
| UMIC | Upper-middle-income country |
| UN | United Nations |
| USAID | US Agency for International Development |
| USTR | United States Trade Representative |
| VL | Voluntary licensing |
| WHO | World Health Organization |

# Introduction

Voluntary licensing (VL) is a strategy for improving access to essential medicines globally. In VL, a patent holder voluntarily grants a license to another manufacturer to produce and sell products that include the patented active pharmaceutical ingredient (API). The licensee, typically a generics manufacturer, is often able to sell its medicine at a significantly reduced price compared to the originator product. VL agreements generally include stipulations such as the royalties to be paid based on the volume of sales, sales restrictions by based on geography, and sale prices.

The use of VL for pharmaceutical access has expanded in recent years, particularly since the creation of the Medicines Patent Pool (MPP) in 2011. It is widely recognized as a successful approach. However, there remains untapped potential to improve existing programs and to license new medicines. Realizing the full potential of VL—through existing mechanisms, such as bilateral agreements and the MPP, or in new ways—could dramatically improve access to life-saving medications and thereby save lives.

In 2006, Gilead Sciences Inc. initiated a program of VL of its antiviral molecule tenofovir disoproxil fumarate (TDF) that is now one of the largest VL programs. By June 2019, more than thirteen million patients in low- and middle-income countries (LMICs) had received generic TDF from a Gilead licensee. Not only was Gilead's VL program for TDF one of the first of its kind—it also contributed to the creation of the MPP and led to other pharmaceutical companies adopting a similar approach for a range of important medicines. In recent years, Gilead has expanded its VL program to include other molecules, including newer HIV therapies as well as sofosbuvir and other molecules used in the treatment of Hepatitis C virus (HCV). The large scope of Gilead's program is unique and unmatched by other companies.

This report, based on interviews and literature reviews, summarizes evidence about how Gilead's VL program improved access to treatment for patients globally and explores which factors may have accelerated or hindered the program's uptake and impact. It presents findings from an evaluation project that investigated the factors that influenced participating manufacturers and medicine purchasers, including comparing VL with alternative intervention strategies, such as voluntary licensing through the MPP, compulsory licensing and no licensing.

The key activities in the evaluation were:

- Consultation on the research questions with experts on intellectual property law and policy
- Literature reviews on VL and alternate strategies
- Interviews with global key informants (KIs), including representatives of the pharmaceutical industry, donor/procurement agencies, and global VL experts
- Reviews of documents related to three country case studies
- Interviews with key informants regarding the three country case studies

The report is presented in four parts: (1) a literature review, (2) input from policy and legal experts, (3) summaries of the consultations with global stakeholders on VL and the MPP and (4) three country case studies. It concludes with some comments and recommendations on moving forward with the use of VL to expand access to medicines. The research was conducted with support from Gilead, and is in part intended to inform the company's ongoing efforts to marry its access and business strategies. In addition, the project demonstrates the feasibility and value for private industry to support rigorous, independent evaluation of its activities. A wide range of other stakeholders can also learn from the

results presented in the report, including those with interests in evaluation, voluntary licensing, and medicines access strategies. These stakeholders may include:

- **Originator pharmaceutical companies** interested in an in-depth examination of a longstanding and successful access program. Companies planning or expanding access programs can benefit from the lessons learned about the benefits of VL and options such as direct VL or licensing through the MPP.
- **Generic pharmaceutical companies** seeking to better understand their industry's prominent role in expanding medicines access and the benefits and challenges they face when engaging in VL agreements.
- **Civil society and patient advocate/activist groups** promoting medicines access strategies.
- **Multilateral organizations, procurement and donor agencies**, and the international medicines access community exploring how to negotiate access strategies to maximize the use of available resources.
- **Governments of countries** that can learn from the country case studies how to select appropriate approaches to medicines access strategies to serve their population's needs.
- **Individuals** interested in, among other topics, program evaluation, transparency, academic partnerships with industry, and qualitative and quantitative mixed methods.

In addition to adding to the body of knowledge about VL for access to medicines, this report highlights the importance of rigorous mixed-methods evaluation in measuring the success of programs.

# Literature Review: Voluntary Licensing

We searched PubMed, Google Scholar, data repositories on intellectual property (IP) and related health topics, and company websites for documentation on VL. Appendix 1 presents the full references for studies on VL that are included in this summary of the literature.

**What is voluntary licensing?**

Voluntary licensing (VL) for medicines is when a patent holder on a product voluntarily offers a license to another entity (usually a generic producer) to produce, market, and distribute the patented product (Amin, 2007). The license may include conditions such as a royalty fee (often 5% of sales), or restriction of countries where the product may be sold, among others.

**Which companies use VL for which disease/medicines?**

VL is predominantly used for medicines for the treatment of HIV/AIDS and the Hepatitis C virus (HCV), with the exception of three novel oral antidiabetics (sitagliptin, vildagliptin, and saxagliptin) given voluntary licensing in India in the late 2000's (Chatterjee et al., 2015). As of 2017, Juneja et al. counted 13 antiretrovirals (ARVs) for the treatment of HIV/AIDS licensed through the MPP from seven patent-holders for sale in up to 112 countries (Juneja, Gupta, Moon, & Resch, 2017).

Patent-holding pharmaceutical companies that have granted voluntary licenses for ARVs to generic producers include Bristol-Myers Squibb (Chaves et al., 2015), GlaxoSmithKline and Boehringer-Ingelheim in South Africa (Hoen, Berger, Calmy, & Moon, 2011), and, of course, Gilead Sciences (Cox, 2012). Major ARVs under VL agreements include atazanavir and tenofovir, and HCV medicines include daclatasvir from Bristol-Myers Squibb and sofosbuvir from Gilead (Assefa, Hill, Ulikpan, & Williams, 2017; Douglass et al., 2018; Grillon et al., 2018).

**Which countries have used VL?**

Low-income countries have frequently benefited from VL agreements targeting large groups of countries: 101 low-income countries in the Gilead Access Program, 110 countries in Bristol-Myers Squibb's atanazavir program, and 112 countries in their daclatasvir program. (Douglass et al., 2018, Medicines Patent Pool, 2015). While these agreements often exclude middle-income countries with high disease burdens (like Brazil, China, Morocco and Thailand (Douglass et al., 2018) or Malaysia (Wise, 2017)), these countries have at different times advocated for their own paths to licensing, such as through the threat of compulsory licensing mentioned below.

**How has the impact of VL been assessed?**

Evaluations generally find that VL correlates with lowered prices, although there are few direct comparisons with the other strategies of tiered pricing, compulsory licensing (CL), patent opposition, and the use of TRIPS flexibilities. Some authors see VL as the preferred method while others recommend VL in combination with the other strategies.

Simmons, Cooke, and Miraldo, in an impact evaluation of Gilead's and Bristol-Myers Squibb's VL of HCV medicines, report 53 to 70 more people receiving treatment per 1,000 diagnosed in countries included in VL agreements compared to those excluded countries. The study provides empirical endorsement of VL as an access strategy, but did not examine medicine price (2019).

Comparing prices for dolutegravir (DTG) between countries with and without VL, Sim and Hill report that "median price in countries excluded from VL agreements ($8,718) was >140 times higher than countries included ($60)," implying effectiveness of VL as a price reduction mechanism (Sim & Hill, 2018). Similarly, Hill and Pozniak report lower prices for countries receiving VL HIV medicines versus those not ($755 per person-year for VL darunavir in Uganda versus $6,539 for non-VL medicines in Tunisia and $6,010 in Jamaica), identifying the exclusion of middle-income countries as the chief problem with VL (Hill & Pozniak, 2016).

Some studies find less impressive price reductions associated with VL. Assefa et al. find generic HCV medicines under VL cheaper ($684-750 per patient treated) than Gilead's branded medicines ($1,200), but note that the costs remain prohibitive in the country contexts; they promote CL and patent opposition as more promising strategies (Assefa et al., 2017).

A few other studies compare VL with other strategies, including CL. Beall and Attaran, examining HIV medicine procurement volume only (rather than pricing), find greater volumes for countries with VL agreements than for those procuring medicines under other legal concepts, including CL, the TRIPS least-developed country waiver, companies' patent non-enforcement policies (in which companies announce their non-enforcement of their patents in certain regions, allowing generic suppliers to operate there without fear of legal recourse) (Beall & Attaran, 2017). The reason for greater volumes are unclear but may include licensees are more likely to seek local regulatory approval, which is often a major barrier to access. Another reason could be that innovators such as Gilead are also more likely to support market development activity (including education, screening, etc.) to support use of VL products in these markets.

In 2015, Walsh et al. credited Gilead's VL for sofosbuvir with lowering prices from a maximum of $100,000 per course to about $300 per month of treatment, although the authors did not rule out the influences of CL, individual country negotiations, and other legal flexibilities (Walsh, Durier, Khwairakpam, Sohn, & Lo, 2015).

Many authors concur that VL could not stand alone without the threat of the more forceful counterpart, CL. Brazil's negotiation with BMS for atazanavir involved the threat of CL and the issuance of a CL, ultimately resulting in VL. The results were major price reductions (up to 49% in a two-year period), considered a successful use of multiple price-reduction strategies (Chaves et al., 2015). Similarly, the strategic combination of CL and VL brought the price of HCV medicines sofosbuvir and daclatasvir from $147,000 for a 12-week course, down to as little as $120 for MSF projects in 11 countries (Wise, 2017).

**What are the legal and theoretical considerations of VL?**

Using theoretical modeling to estimate costs through 2028, Juneja et al. project a cost-benefit ratio of 1:43 for VL through MPP, which means for every one US dollar spent on MPP, the global public health community saves USD 43 (2017). Another modeling study finds VL preferable to CL for reducing prices without discouraging innovation (Chatterjee et al., 2015).

In a large analysis of access mechanisms, Grillon et al. confirm that VL programs lower prices while lamenting their neglect of middle-income countries (2018). One author criticizes VL programs for missed opportunities such as the exclusion of middle-income countries, excessive restrictions on the terms of VL including restrictions on active pharmaceutical ingredients, lack of transparency of agreements, and the limited number of agreements emitted (Pascual, 2014).

Brook Baker (2018) provides an in-depth analysis of voluntary licensing by Gilead and the MPP. He argues that there are two general types of VL agreements: "purely commercial" licenses that have long

been used in the pharmaceutical industry, and new "access" licensing, which actively seeks to promote access to medicines while also satisfying commercial interests. The author evaluates the public health impact of the terms and conditions of each licensing agreement, including: API restrictions (bad for access), patents on pipeline products (unclear whether good or bad for access), direct and indirect territorial restrictions (bad for access), and allowing CL and patent opposition (good for access). The author concludes that VL, especially access licensing, is an important part of increasing medicines access. However, he cautions that it does not end the problem, nor does it exist in a vacuum separate from other access strategies.

**How does VL compare to other possible strategies?**

VL contrasts with compulsory licensing (CL), in which a national government issues a license for a medicine to a producer in defiance of a patent-holder's IP rights. In practice, countries often leverage the threat of compulsory licensing to motivate the release of voluntary licenses on key medicines, which some see as an appropriate balance between social good and the protection of IP rights (Raju, 2017). Notable uses of the threat of CL to gain VL are: Brazil's negotiations over atazanavir with Bristol Meyers-Squibb in 2007 (Chaves, Hasenclever, Osorio-de-Castro, & Oliveira, 2015); Malaysia's deal with Gilead over sofosbuvir in 2017 (Douglass et al., 2018; Intellectual Property Watch, 2017); and, several cases in India (Chatterjee, Kubo, & Pingali, 2015). While the strategy is controversial, empirical evidence indicates that countries with mature patent systems are more likely to declare CL for pharmaceuticals (Son, 2019), and modelling suggests that CL is associated with increased welfare for developing nations, despite the feared impact on innovation (Stavropoulou & Valletti, 2015).

A minority of generic manufacturers forego licensing, including Pharco in Egypt, Beker in Algeria, and Pharma5 in Morocco. These companies are producing daclatasvir without a license (Grillon et al., 2018), considered by patent-holders to be unauthorized or unlicensed generics. The impact of this model on pricing has not been closely studied.

Another variation is non-assert declarations, such as that granted by Boehringer-Ingelheim to Aspen Pharmacare in South Africa, in which a company conditionally states that it will not enforce its patent (Beyer, 2013).

Tiered pricing strategies are common but understudied. Authors voice concerns that these strategies are under the exclusive control of patent-holding companies, which apply them to an arbitrary list of low-income countries; these are therefore not seen as acceptable access strategies (Chaves et al., 2015).

**How does the Medicines Patent Pool use VL?**

VL granting authorities fall into two main categories: patent-holding pharmaceutical companies, and the Medicines Patent Pool (MPP), a group established through UNITAID in 2011 as a "clearinghouse" for patent information to facilitate voluntary licensing (Bermudez & Hoen, 2010; Cox, 2012).The MPP's licensees are credited with distributing 22 million patient-years of treatment, thereby saving USD$1.06 billion globally. The organization's charter covers HIV, HCV, and tuberculosis, although a 2019 feasibility study proposes new categories including cancer and antimicrobials (Burrone et al., 2019). While the organization's impact has been studied, there are no published comparisons between MPP and industry-led VL programs.

## Consultations with Policy and Legal Experts

At the outset of the study, we sought input and recommendations on the study via email from 14 experts on IP and legal advocacy. Common themes from respondents were incorporated into the study design and interview guides. Six individuals responded with contributions, including two from U.S. law schools (St. Louis University and De Paul University), two independent consultants, and two from international civil society organizations (Médecins sans Frontières and I-MAK).

All six experts recommended reframing the core study question. While originally we had planned to compare direct VL with relevant alternatives (CL; other forms of VL, e.g. MPP licensing; no licensing), they recommended instead exploring the interactions and relationships among all of the strategies. This approach dovetailed with the literature review findings as well. In the real world, these strategies are interconnected, not discrete choices.

We describe this as the "ecosystem" model of licensing (as juxtaposed against a "discrete alternatives" model). This reframing made our interview topics more nuanced—and the questions sometimes more difficult to answer. Questions emerging from these consultations included:

- How do other interventions (e.g. the MPP, government pressure through the actual or threatened use of flexibilities, patent oppositions, and the emergence of new manufacturers in other jurisdictions) impact originator-led licensing programs?
- What choices do scientists or drug suppliers make because of the VL program that they might not have made in the absence of that program?
- Would CL actually have occurred in the absence of the VL program? Would it have provided wider access at lower costs?
- Does manufacturing without a license encourage other manufacturers to do the same? Does it encourage them to seek licenses? How else might no-license have impacted the other strategies chosen by companies?

The legal experts' input led us to define a typology of voluntary licensing, presented in Table 1. Traditionally, manufacturers have entered 1-to-1 licensing arrangements where the originator company signed a voluntary license with one other company. An example is Roche signing a voluntary license with Emcure for trastuzumab, a biological medication for the treatment of breast cancer.

The Gilead Access Program was distinct from the traditional bilateral licenses when it was initiated in the sense that it established voluntary licenses with multiple generic companies to enable competition and reduce prices. The MPP is distinct because the licenser is not a manufacturer but an organization that coordinates the sharing of patents for IP. The originator company issues its license into the patent pool, from which other companies can license out.

The legal experts' input also contributed to the background literature review, the recruitment of other interviewees, and the selection of country case studies.

*Table 1: Typology of Voluntary Licensing*

| Type | Characteristics | Example |
|---|---|---|
| **1-to-1:**<br>M**anufacturer to one manufacturer licensing** | • Goal is to have only 1 generic enter market<br>• Purely commercial (Baker 2018)<br>• May or may not be exclusive | Roche – Emcure for trastuzumab |
| **Multilateral licensing:**<br>M**anufacturer to multiple manufacturers** | • Goal is to have multiple generics enter market<br>• Direct VL between 1 patent holder and many generic producers<br>• May be more bilateral than 1-to-1 licensing<br>• Non-exclusive | Gilead Access Program |
| **MPP licensing:**<br>One licensing agency to one or more manufacturers | • Goal is "access" or "public health" licenses<br>• pluralistic in detail<br>• broad geographic scope<br>• transparency<br>• preservation of TRIPS flexibilities<br>• "not free of commercial motivations" for patent-holders or generics (Baker 2018) | Merck-MPP-multiple producers |

# Facilitators and Barriers of the Gilead TDF Access Program

## Global-Level Key Informant Interviews

We interviewed 19 global key informants, including representatives from multilateral agencies (such as WHO), procurement and donor agencies (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and USAID), generics manufacturers, the Medicines Patent Pool (MPP), and Gilead Sciences. Table 2 lists the agencies and companies whose representatives participated in the Global Key Informant Study. All key informants (KIs) were recruited through informant-driven sampling. Informants were first contacted via email to arrange interviews, which were then conducted via phone or web-based platforms between March and June 2019.

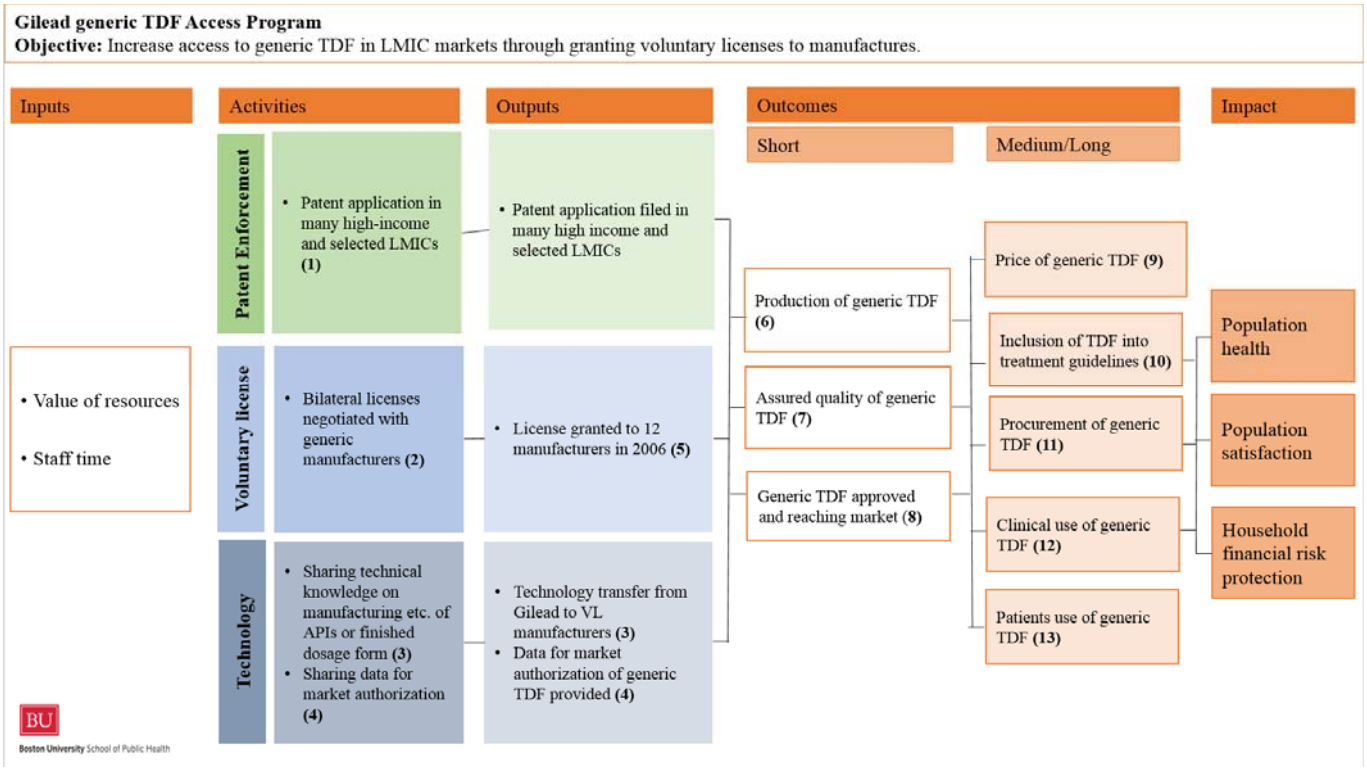
The objective of the interviews was to understand the KIs' perspectives and experiences with the Gilead Access Program and other medicines access strategies. Interviews were conducted based on interview guides (included in Appendix 2) prepared using background research, consultations, and document review. However, we did not stick rigidly to the guide while conducting the interviews. Two members of the research team conducted each interview, taking notes that were compared later for completeness and accuracy. Interviews were not audio-recorded. Interviewees were asked follow-up questions via email as needed.

*Table 2: Interviewees who contributed to the Global Key Informant Study, by Agency (N=20)*

| Type of Institution | Companies/Agencies | Number of Interviewees |
|---|---|---|
| **Licensor (Originator Pharmaceutical Company)** | Gilead Africa | 4 |
| | Gilead Asia Pacific | 1 |
| **Licensees (Generics Pharmaceutical)** | Aurobindo | 1 |
| | Cipla | 1 |
| | Hetero | 1 |
| | Mylan | 1 |
| | Emcure | 1 |
| **Donor/Procurement Agency** | CHAI | 2 |
| | USAID | 1 |
| **Civil Society Organization** | World Health Organization's Global Price Reporting Mechanism (GPRM) | 1 |
| | MPP | 4 |
| | i+solutions | 1 |

The results from these global-level KI interviews (and related document reviews) are presented collated according to the activities, outputs and outcomes enumerated in the logic model for the Gilead Access Program for TDF (Figure 1). For each numbered element, we describe the facilitators and/or barriers mentioned by interviewees. "Facilitators" are factors that, according to the KIs, promoted the implementation or desired impact of the Access Program. "Barriers" as described by the key KIs are factors that hindered the implementation or desired impact of the Gilead Access Program.

*Figure 1: Logic model of Gilead's TDF Access Program*




***Notes:***

- The **numbers** in the logic model correspond to the items described in the text.
- **Activities** are defined as actions that are under Gilead's direct control.
- **Outputs** are the immediate results of the activities.
- **Outcomes** are the results of the program but not under Gilead's direct control.

***Source:*** Authors' elaboration of the logic model developed by the Access Observatory on Licensing Agreements.[1]

Gilead filed patents related to TDF in a large number of high-income countries and selected LMIC, including India and Thailand (item 1).[2] The main activity of the TDF access programs was the negotiation of bilateral voluntary licenses (2) that included technology transfer agreements from Gilead to the generics manufacturers (3). Another Gilead program activity was the registration of originator products in a large number of low income countries (4). The main output of the access program was the signing of voluntary licenses with 12 manufacturers (5). Key short-term outcomes of the program are production (6), quality assurance (7), market registration (8) and the prices that VL licensee manufacturers charged for generic TDF. Medium- and long-term outcomes are inclusion of TDF in treatment guidelines (9), procurement (10), clinical (11) and patient use (12) of TDF.

[1] Access Observatory. Harmonized logic models. Available at: https://docs.wixstatic.com/ugd/37a51e_f9250725fdd541a89e11bf5e557d52ee.pdf

[2] The number in brackets correspond to the items in the logic model.

## Factors influencing the Gilead TDF Access Program

In this section, we present the main factors that influenced Gilead's TDF Access Program, organized by activity, output and outcome of Gilead's TDF Access Program. Some KIs were asked to compare a specific feature of the TDF Access Program with the Sofosbuvir Access Program—therefore, we have also included text boxes to highlight comparisons with the Sofosbuvir Access Program.

### *1. Filing TDF patent application(s)*

Gilead filed patent applications for TDF in many countries. India was one of the most important of these since it is home to a large number of manufacturers capable of producing TDF and fixed-dose formulations, in particular TDF in combination of emtricitabine (FTC). Additionally, Indian generic manufacturers have the capacity to produce TDF and combination products with a level of quality capable of meeting stringent regulatory authority (SRA) standards, including the World Health Organization Prequalification (PQ) Program. A number of generics manufacturers in India were interested in obtaining a voluntary license from Gilead to produce TDF because Gilead had filed a patent application. If Gilead had not filed for a patent in India, generics manufacturers would have been able to produce TDF without obtaining a voluntary license. At least one manufacturer did in fact produce TDF without signing a voluntary license—Gilead interviewees noted that this manufacturer was "unauthorized."

### *2. Offering a bilateral voluntary license to one or more manufacturers*

**Facilitator:** Gilead's interest in promoting TDF in LMIC markets

An important motivation for Gilead to offer a voluntary license was to provide other companies that did have a market presence in LMICs the opportunity to sell TDF, Gilead's product, without threatening Gilead's market penetration in high-income country markets. While Gilead has no commercial presence in many LMICs, the large Indian manufacturers are established sellers in many LMICs. Their capabilities—in registering, supplying, and selling the product—were key to overcoming supply-side barriers that Gilead faces in low-income markets.

**Facilitator:** Gilead's interest in increasing competition resulted in giving VL to multiple manufacturers (several in India and one in South Africa)

In 2006 Gilead determined that by issuing licenses to 12 companies, it could ensure that at least four would follow through on all the necessary steps and ultimately enter the market. One interviewee explained that the reason Gilead wanted to license products to multiple companies (rather than local manufacturers in several countries) was to foster competition among the Indian manufacturers operating in different country markets. Licensing only local manufacturers in certain markets would result in a lack of competition and therefore higher medication prices.

### *3. Technology transfer from the originator to the generics manufacturers*

**Facilitator and barrier:** The scope of Gilead's technology transfer

Technology transfer was not uniformly seen as a key element in the license and to the success of the Gilead Access Program. Some manufacturers confirmed that Gilead's transfer of technology and know-

how were essential to beginning TDF production. Several other interviewees, including non-manufacturers, did not see the transfer as especially important given the existing advanced technical expertise among certain licensees.

A representative from Gilead confirmed that on occasions when a licensee sought clarification Gilead had provided additional technical support as deemed appropriate; however, some interviewees reported that in their cases Gilead had not provided technical support to generic manufacturers to improve production processes.

However, VL *without* technology transfer is not viable if a generics manufacturer does not have the capacity to produce the medicines. Technology transfer can go either way: from Gilead to the VL manufacturer to inform and enable knowledge about the product, and through "back-licensing" from the generic manufacturers back to Gilead to improve production methods. The KIs did not mention specific instances when this had happened.

A Gilead representative explained that Gilead's requirement to report improvements and seek a license to use such improvements was not aimed at enhancing Gilead's ability to improve its own production. Instead, this serves to mitigate the risk of Gilead being blocked from using licensees' process improvements that Gilead might have developed in parallel but not necessarily patented.

### *4. Market registration by Gilead in countries where generic manufacturer sells product*

**Facilitator:** Gilead's registration of originator product in many LMICs

An in-country barrier to access to a medicine produced under voluntary licenses can be market authorization. If the process of market authorization takes a long time, it can hinder sales in the country. To enable VL manufacturers to register generic TDF using Gilead's originator product clinical trial data, Gilead had to first register its TDF products.

This was particular relevant in South Africa and Thailand. The licensed manufacturers would benchmark (i.e., use bioequivalence data) to show that their product was interchangeable with the approved Gilead product. A Gilead representative explained that for some countries (such as India, Nigeria, Vietnam, Indonesia and Philippines) the country's own legislation may require local clinical data. Obtaining local clinical trial data can delay registration. In Vietnam and elsewhere, Gilead has successfully negotiated with regulatory authorities to provide the generic manufacturer with data.

According to several key informants, Gilead registered TDF in many countries to support licensed manufacturers registering their generic TDF produced under a voluntary license. Manufacturers did not mention a lack of market authorization by Gilead as a problem.

It is noteworthy that a few interviewees mentioned that certain countries' procurement agencies can request a procurement waiver from the Medicines Regulatory Authority if a product has not yet been registered in the country…provided it has received WHO Prequalification and is imported using Global Fund support.[3] However, the waiver is only a temporary measure while the Medicine Regulatory Authority reviews the product registration application.

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[3] Despite the temporary procurement waiver, it is still necessary to register the product in the country. The medicine regulatory authority requires more information than is included in the WHO Prequalification which the manufacturer will need to make available.

### 5. *Signing bilateral licensing agreement(s) with Gilead*

**Facilitator**: Incentives for generic manufacturers to have a bilateral relation with Gilead

Overall, informants from TDF manufacturers in India described having complex relationships with Gilead, reporting both competitive and collaborative dynamics. Both types of companies complemented each other's strengths and described working as a team with the goal of bringing access to more countries.

The Indian generics TDF manufacturer informants expressed their strong preferences for having a direct relationship with Gilead, citing flexibility and the opportunity to open new territories that this affords them. Direct negotiations with Gilead also provide the manufacturers with opportunities to discuss future portfolios and the possibility of making the API.

One manufacturer reported that they had succeeded in negotiating a low royalty from Gilead. However, this low royalty was then included in the licenses to all the other manufacturers. The negotiating manufacturer was disappointed not to be able to keep its advantage over the other generic companies, but accepted that Gilead provides all manufacturers with the same terms in its direct license. Some interviewees noted that royalties paid to the originator were so small as to be negligible or had even disappeared.

Interviewees pointed out different capacities between Indian manufacturers and Gilead. The Indian manufacturers reportedly were willing and able to make process improvements to the production of TDF through know-how and economy of scale in order to market in LMICs. At times they would bring education and awareness to countries' Ministries of Health. Some Indian manufacturers pointed to the tasks undertaken by Gilead that are difficult for them to perform, such as patenting products, performing clinical trials, and gaining FDA approval. Manufacturers reported that the continuity of Gilead's and their own staff members have allowed for strengthening long-standing relationships.

### 6. *Production of the generic product under bilateral voluntary license*

**Facilitator:** Demand for generic TDF

Production of generic TDF products is the intended outcome of the VL program. Whether a generic manufacturer that signs a TDF VL can in fact manufacture the product depends on a variety of factors. Interviewees highlighted that global and sustained demand for the product is a very important factor influencing manufacturers' interest in and willingness to invest in optimizing production.

Donors play an important role in creating demand and shaping the TDF market; they may differ in their approaches to these activities. For instance, an interviewee explained that CHAI invests significantly in shaping markets, such as fostering TDF's market entry in the early 2000s. One interviewee explained that after a competitive bidding process, CHAI partnered with Matrix/Mylan, which had recently been licensed to produce TDF, to "kick-start" the cycle between supply and demand. CHAI worked with Howard University and an institution in China to improve the manufacturer's efficiency and lower production costs. In another instance, CHAI representatives brokered an agreement with UNITAID to purchase TDF for the entire country of Zambia, guaranteeing a market. For the fixed-dose combination efavirenz/emtricitabine/tenofovir, Mylan was the first generic on the market by almost three years while reducing the price, an accomplishment that some attribute to their partnership with CHAI and its market-shaping ability. While donors like CHAI championed VL, interviewees mentioned that PEPFAR

was slow to adopt generics and persisted in preferring originator medicines long after the VL program was established.

**Facilitator:** Size of the profits from generic TDF sales

Interviewees identified the profit margin on generic TDF as another significant factor influencing the decisions of licensees whether to proceed with producing TDF. Although the profit margins for first-line ARVs such as TDF are notably smaller than for some second-line and pediatric products, the larger demand volume for first-line ARVs can compensate for this lower profit margin. This presents an attractive business case for generics manufacturers. In brief, since production of TDF by generics manufacturers is an outcome of the VL program, several interviewees identified production [yes/no] as well as volume of production [units] as important indicators for assessing whether the VL program met its objectives.

**Comparator: Sofosbuvir Access Program**

**Barrier: Lack of donor funding**

In the absence of large donor organizations funding hepatitis C medicines, interest on the part of government programs, including the available financial resources, are determining the demand for sofosbuvir. Compared with TDF, which was championed by CHAI, it has been much harder to make predictions about demand volume and secure investments in product development.

### *7. Quality assurance of production*

**Facilitator and barrier:** Gilead's requirement of WHO PQ of generic TDF

Donors concerned about ensuring the quality of TDF produced by Indian manufacturers cited WHO PQ as an important consideration. Gilead's license required Indian TDF manufacturers to obtain WHO PQ or FDA preapproval for their products ("Licensee shall apply for WHO pre-qualification or FDA conditional approval no later than the first anniversary of the Effective Date"[4]). Several Indian TDF manufacturers confirmed the importance of the requirement for quality assurance built into the license.

Some interviewees noted that non-VL manufacturers had briefly entered the TDF market, undercutting existing prices with low quality products. However, after disrupting the market they quickly left without sustainable profits. The entrance of low-quality products into the market can hinder the uptake of higher-priced quality-assured products. Some interviewees from manufacturers mentioned that low-priced, non-quality-assured generic TDF could make the higher-priced WHO PQ products less competitive. If all buyers would require quality-assured products, no market would exist for low-quality products. One key informant pointed out that some countries' legislation actually hinder procurement of higher-priced, quality-assured TDF products when the procurement laws stipulate that the lowest-priced product has to be purchased.

Obtaining WHO Prequalification is an investment and requires high technical standards. In general, smaller manufacturers that have not already invested early in Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP) may try to obtain WHO PQ but often cannot obtain it because compliance

[4] Available at: https://www.gilead.com/-/media/files/pdfs/other/originaltdflicenseagreement.pdf?la=en&hash=8A28DA24E3B6A75D190561DD52C3E865

with these standards would require a major investment. As a result, large Indian generics manufacturers that had already received market approval by SRAs were in a better position to obtain WHO PQ for TDF right at the start of Gilead's VL program. Moreover, interviewees emphasized that WHO PQ is not a one-time test, but requires ongoing compliance, further reducing small companies' chance at success in this domain.

Several Indian manufacturers that signed the VL for TDF had adopted GMP and GCP in the 1990s. Thus for many it was possible to obtain WHO Prequalification for TDF. WHO PQ inspectors almost always produce a list of issues for the manufacturers to fix after the first inspection visit, including for the Indian TDF generic manufacturers signing Gilead's VL requesting WHO prequalification. The WHO PQ inspectors found problems and requested manufacturers to address them, which they did to receive PQ.

**Comparator: Sofosbuvir Access Program**

**Barrier: Absence of the WHO PQ requirement**

Contrastingly, Gilead's voluntary sofosbuvir license did not include the requirement of quality assurance. According to one key informant, Gilead added this requirement later on. Some interviewees confirmed that the absence of sofosbuvir WHO PQ was a concern.

### *8. Market registration of generic TDF products in countries included in the license*

**Facilitator:** Market registration of originator product

As mentioned above, in ideal situations, Gilead registers its product first in a given market. The licensed manufacturer then benchmarks to show that their product is interchangeable with the Gilead product when they register their generic products.

**Facilitator and barrier:** Promotion of the originator product

Since market registration of generic TDF products is a key outcome of the VL program, some interviewees saw it as an indicator to measure whether the VL program was achieving its objectives.

One key informant explained that licensed generic manufacturers typically do not do "market development," such as investing in healthcare provider training and patient education about a new generic medication in LMICs. This saves generic manufacturers the money and effort involved in making a new version of a medicine known to prescribers and patients. On the other hand, lack of market development avoids creating brand preference in private markets. In contrast, Gilead reported it significantly invested in educating physicians and patients about TDF (although patient advocates in some countries disagree and said that more education was provided by local NGOs). Gilead was also very active in lobbying governments to approve and incorporate TDF into treatment guidelines. Pricing of generic TDF by manufacturers

**Facilitator:** Lower prices for generic TDF

Originator products are usually the highest priced product when compared to generic versions in different markets. In the absence of the originator product in LMIC markets, the key informants felt that Gilead's granting of TDF voluntary license to 12 companies simultaneously introduced price competition among these companies and this resulted in even lower prices than the companies would have set if fewer licenses had been awarded.

Large procurement agencies have bidding processes in place that accept applications from previously-qualified manufacturers that produce generic TDF under VL. Interviewees noted that TDF supply contracts are awarded not only based on price but also depending on how much volume can be made available by the time needed and the shelf-life of the medicine. (Quality assurance is taken for granted in this bidding process. Prior performance of the TDF supplier was not mentioned by key informants but is taken into consideration too.)

One interviewee explained that by 2019, after nearly 15 years of ARV production by generic Indian manufacturers, two large generic manufacturers have come to dominate the ARV market. This market concentration among two TDF producers was concerning to some interviewees, who thought it could result in lack of competition and thus higher prices, lower production and decreased TDF access. Some argued that because TDF is part of first-line combination ARVs, there should be at least four or five manufacturers. While there was no agreement on the "right number" of licensees, some proposed that there should simply be enough manufacturers for the market to remain dynamic; others said it mattered more how licensees were selected and promoted.

One key factor related to setting the price for generic TDF was the cost of the API. In the early 2000s, the production of TDF's API was not very efficient. It was not until investments by donors to optimize production of the API were made that Indian manufacturers were able to product TDF at lower costs. Some interviewees warned that using GDP[5] as the determining factor in pricing TDF products, whether for an originator or a generic medicine done by manufacturers, sets prices higher than the majority of a country's population can afford as a result of large inequities among population groups within a country.

### *9. Inclusion in Standard Treatment Guidelines and Essential Medicines Lists*

**Facilitator:** Inclusion of TDF in first-line regimens in Standard Treatment Guidelines

Key informants explained that the WHO Standard Treatment Guidelines (STG) had a significant influence on procurement decisions in countries and, hence, on the global market for generic ARVs including TDF. Agencies that support countries in procuring ARV medicines for their national HIV programs use the WHO STGs to advise them which products to choose.

Interviewees noted that price was an important criterion in the WHO's decision about which medicine to include in the STG. In particular, price is linked to whether the medicine is recommended as first- or second-line. TDF was not initially included as a first-line antiretroviral in the WHO STG since the price was considered too high. It took lobbying from several stakeholders for WHO to include TDF as first-line medication in 2007. In the same year, TDF was included in the WHO Essential Medicines List.[6] It took several more years to see TDF included as a first-line ARV in many countries.

### *10. Procurement*

**Facilitator:** Procurement of TDF by large donor organizations and national HIV programs

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[5] Interviewees mentioned GDP but depending on the case GNP may be used to set product prices.

[6] The reason for not including TDF in the 2005 EML was that Gilead insisted on confidentiality application and the Committee deferred the application.

Informants at several agencies described that product selection plays a major role in shaping ARV markets and hence influencing demand for generic TDF. Actors involved in procurement suggest products for countries to purchase based on analyses of WHO and country treatment guidelines, as well as countries' burden of disease, income level, which suppliers have WHO prequalification, and other factors. Interviewees regretted that the lack of coordinated demand forecasting forces manufacturers to produce medicines without knowing whether they will be able to sell them. Interviewees from donor and procurement agencies, including the PAHO Strategic Fund, explained that guaranteeing a specific volume of medicine was another important mechanism to achieving lower prices of TDF, along with guaranteeing delivery time of the product. These factors are important to provide for a predictable market for VL Indian generic manufacturers.

**Barrier:** Preference for the originator product

Donor and civil society representatives stressed that while they can make product recommendations, product selection ultimately lies with countries, and these are constrained by IP and other legal considerations (including whether the country is within a VL territory, the extent and kind of patent coverage, and the medicine's registration status). Country governments, like individuals, may be biased towards originator medicines to the detriment of the medicines budget. One reason for brand bias is lack of knowledge in Ministries of Health about IP regulations related to medicines and often also in Patent Offices and Regulatory Authorities.

**Comparator: Sofosbuvir Access Program**

**Barrier: Patent protection of API of a fixed-dose combination of sofosbuvir**

Fixed-dose combination (FDC) or combination therapy requires that all medicines included in the combination need to be available in the country. In the case of sofosbuvir, procurement agencies and countries face difficulties when sofosbuvir is registered as a generic medicine in the country but the other required medicines within the combination are not available as generic versions due to patent protection.

## The Medicines Patent Pool

Beginning in 2011, Gilead signed an agreement with the Medicines Patent Pool (MPP) to license selected patents, including TDF. As mentioned above, the MPP was created in 2011 as a public health-focused organization with a mission to "increase access to, and facilitate the development of, life-saving medicines for LMICs through an innovative approach to voluntary licensing and patent pooling." The agency, which is funded through Unitaid, came into being a few years after Gilead's VL access program was established. It measures its impact in terms of savings on medicines, patient-years of medicines provided, the total number of territories, new territories, and the number of territories included in agreements that are excluded from bilateral agreements. The MPP does not measure success by the number of licensees; while that is a program output, more licensees does not necessarily mean greater success in terms of access to medicines and improvements in public health.

Licensing of TDF was the first effort by the MPP and remains its biggest program; in a 2019 *Update on progress of MPP sublicensees*, 90-95% of MPP's savings impact is attributed to TDF. Gilead's agreement with MPP does not preclude individual licensing by Gilead as well. Further, the licenses issued by the MPP are essentially tripartite agreements among Gilead, MPP and a generics manufacturer. All VLs issued by the MPP for a given medicine in a given territory are identical to each other.

Due to the centrality of TDF in the MPP, we included its representatives in the global level interviews (as well as asking the other KIs for comments on the impact of the MPP with regards to TDF). Their comments are summarized.

### 1. *What an MPP license offers that a direct license does not*

**Expansion of territory of licenses**

All MPP informants believed that their agency initially offered more desirable licensing terms to manufacturers. Interviewees highlighted the inclusion of a CL clause, allowing licensed manufacturers to sell outside of agreement territories when countries have issued a compulsory license. MPP staff pointed out that that this type of CL clause, which originated with MPP licenses, was then adopted in Gilead's HCV voluntary licenses, showing the influence of pro-access policies from the MPP on the Gilead Access Program. The ability to supply to countries that declare CL was seen as attractive for manufacturers and a boon for countries' medicines access.

All manufacturers acknowledged the relevance of the MPP for their ability to get large pharmaceutical companies to license their technology and to bring generics and originators together. The terms of an MPP license apply to all manufacturers, ensuring a level playing field that may harm generics companies' commercial interests but is good for lowering prices.

One manufacturer reported that the MPP was proactive in approaching manufacturers possibly interested in taking a license. The MPP informed the manufacturer about the creation of the MPP and how to obtain a license. This manufacturer explained that their company chose an MPP license over a direct license because of a clause allowing sales in countries without patent coverage, a freedom not allowed in Gilead licenses at the time.

**Unbundling**

Interviewees saw unbundling as a key MPP accomplishment. Unbundling allows manufacturers to choose between the licenses, rather than being forced to sign licenses for all the medicines offered by a manufacturer. This provision made it possible for manufacturers to choose not to license TDF when its patent was denied in India and its patent coverage was weak worldwide. Manufacturers were then able

to sign patents for other medicines offered by Gilead through MPP, without being obliged to sign on to the whole "bundle." This allowance was seen as an important achievement for MPP's negotiation team.

**Quality assurance**

MPP's universal requirement of WHO Prequalification, FDA Preapproval, or other Stringent Regulatory Authority approval for all licensees was seen as setting an appropriately high bar for licensees. While not necessarily attractive to manufacturers, informants saw this as key to ensuring quality medicines, upholding generics' reputation, and in line with their public health mission.

**Follow-through**

Beyond licensing conditions, informants emphasized the importance of follow-through for their licensees' success. Rather than "just giving [the technology] away," the MPP provides a package of services including license management, demand forecasting based on WHO guidelines, technical consulting to help roll out production, assistance with registration in new territories, and ongoing support on business, regulatory, and technical aspects. MPP informants considered that this support helps licensees' products get to market faster, as well as saving Gilead time and effort in doing this themselves. As mentioned previously, not all manufacturers required technical support or assistance and saw this as an advantage. The MPP regularly meets with manufacturers to get feedback and identify challenges and opportunities. Manufacturers explained that UNITAID has oversight over the MPP and ensured adherence to organizational governance, which some perceived as heavy and burdensome. Interviewees explained that the MPP still has to go back to the license owner for every decision, slowing down processes. One manufacturer switched from Gilead to the MPP, then back to Gilead, citing the greater flexibility and ease of communication of direct agreements with Gilead.

### *2. Challenges faced by the MPP*

**Territories**

Informants identified territories as the most challenging aspect of license negotiations for the MPP. Upper-middle income countries (UMICs) in particular were battlegrounds between originators and generic companies. Gilead sees countries like Brazil, China, and Mexico as their greatest source of future revenue; meanwhile generic licensees seek access to these wealthier markets in addition to the LMICs that they have been supplying. At the same time, advocates express significant concerns about large inequalities in UMICs, begging the question whether brand and generic medicines can split country markets. Nonetheless, MPP boasts a large and growing list of 116 territories (as of 2017).

**Reporting**

MPP informants admitted that their reporting requirements can be burdensome for licensees who may be used to fewer demands from Gilead. This was considered simply a necessary part of the agency's commitment to transparency and public health, not a strong disincentive for licensees.

## Country Case studies: Thailand, Zambia and Ecuador

Another set of KI interviews was conducted to gather data to prepare profiles of three countries' experiences with creating access to TDF. The three countries were selected to show a range of experiences possible when VL and other access strategies are used in different combinations. As shown in Table 3, the three countries profiled—Ecuador, Thailand and Zambia—represent different phenotypes in terms of the speed and success of TDF uptake.

The selection of these three countries captures variation in geographical region, when the Gilead VL was made available, the nature of the domestic pharmaceutical industry, and the speed and volume of uptake of tenofovir, among other features. For example, Ecuador and Thailand are both upper middle income countries, while Zambia is a lower middle income country. Thailand has a domestic pharmaceutical industry with increasing capabilities to produce WHO-prequalified antiretrovirals; Ecuador's domestic industry is comparatively smaller, with lower capability to produce antiretrovirals, while Zambia has no relevant domestic pharmaceutical industry. Zambia is facing a generalized HIV epidemic; Ecuador's is a concentrated epidemic and Thailand has a higher prevalence than Ecuador but still considered a concentrated epidemic. Each country has different political structures, civil society and regional affiliations.

In the following sections, we present each of the three cases individually, with a focus on the contextual elements that served as either facilitators or barriers to access to generic TDF for their populations. Perhaps the most evident finding from the case studies is their variation and the importance of the unique combination of contextual factors in determining the trajectory of the rollout of TDF. VL clearly enables the creation of access to a patent-protected medication—as soon as national stakeholders, including policymakers, health care providers and patients, are educated and prepared to adopt the new medication. Lack of VL, as seen in Ecuador, limits the local stakeholders' options and they turn to other, and in many cases less-desirable, alternatives, including maintaining the status quo of insufficient access.

*Table 3: Overview of features of country cases*

| | **Geographical region** | **Date of Gilead VL program inclusion** | **Domestic antiretroviral medicines production** | **Volume of tenofovir uptake before 2011** | **Speed of tenofovir uptake before 2011** |
|---|---|---|---|---|---|
| **Zambia** | Sub-Saharan Africa | 2006 | No | Large volume of TDF | Very quick uptake |
| **Thailand** | Southeast Asia | 2006 | Yes | Medium | Slow uptake |
| **Ecuador** | South America | 2011 | Very few manufacturers | Nearly none | Nearly no uptake |

The data for the three case studies that follow are taken from material collected via interviews with country-level key informants in each country as well as document reviews. Informants from different sectors (see Table 4) were contacted via email to arrange interviews, later conducted via phone and web-based platforms. The objective of the interviews was to understand key informants' perspectives and experiences relative to the Gilead Access Program and other access strategies such as direct voluntary licensing, VL via MPP licensing, compulsory licensing, and no licensing.

*Table 4: Country Case Study Interviewees' Institutions*

| Country | Government | Pharmaceutical | Multilateral | Civil Society |
|---|---|---|---|---|
| **Thailand N=6** | Government Pharmaceutical Organization | Gilead Sciences | WHO Prequalification Program (2) | International Health Policy Program<br><br>AIDS Access Foundation |
| **Zambia N=7** | Ministry of Health | Gilead Sciences (4) | Unitaid | CHAI |
| **Ecuador N=7** | Ministry of Health (3) | | Strategic Fund, PAHO | Fundación Kimirina<br><br>Coalición Ecuatoriana de Personas Viviendo con el VIH |

Each of the following case studies includes a brief overview of the introduction of TDF into the country and a description of the country's situation. The points in the overview are then elaborated in more detail, beginning with a table of background data regarding the country's population, the status of the HIV epidemic and health system in the country, and the relevant patent situation. It also presents a timeline events related to the introduction of generic TDF into the country. Then it discusses the key facilitators and barriers to the creation of access to TDF in the country as described by the interviewees. The timelines for all three countries are also presented in Table 5 below.

*Table 5: Timeline of Key Events*

| Year | Ecuador | Zambia | Thailand |
|---|---|---|---|
| **2002** | Ecuador requested CL for zidovudine + lamivudine (conbivir) from GSK→leads to price reduction from $350 to $60/month | | |
| 2006 | ***Not*** **included in Gilead VL for Tenofovir** | **Included in direct Gilead VL for TDF** | **Included in Gilead's direct VL territories for TDF**<br><br>Issues CL for efavirenz to GPO |
| **2007** | | **MoH introduces TDF as part of first-line therapy** (becoming the first African country to use the drug on a wide scale) | Issues CL for lopinavir/ritonavir<br><br>Contracts with Ranbaxy to import efavirenz |
| **2009** | Compulsory license decree | | |
| **2010** | Issues CL for Eskegroup SA, a local distributor of Cipla, to import API for ritonavir, paying royalties to the originator, Abbott. | | **TDF as first-line treatment added to National Treatment Guidelines** |
| 2011 | **Included in MPP license for TDF** | **Included in MPP for TDF** | **Included in MPP license for TDF** |
| **2012** | **TDF as first-line treatment added to National Treatment Guidelines**<br>CLs issued for abacavir/lamivudine and ritonavir + lopinavir | | |
| **2013** | | Generic Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) from Mylan introduced as first-line therapy | **GPO begins producing TDF** |
| **2014** | *Not* included in Gilead VL for Sofosbuvir[7] | Included in direct Gilead VL for SOF | |
| **2017** | | | Included in Gilead's VL for SOF |

[7] https://www.gilead.com/-/media/files/pdfs/other/form%20ar%20hcv%20license%20agmt%20gild%2011202017.pdf?la=en

## THAILAND

### Overview

Thailand has availed itself of both voluntary and compulsory licenses for anti-retroviral medications. Regarding tenofovir in particular, Thailand was included in the TDF VL program from its inception in 2006, and imports the medication for use in public sector health institutions. Private health institutions use Gilead's branded originator products.

The TDF VL program has allowed the Thai government to import WHO PQ quality-assured TDF-containing products from India. Since 2010, TDF has been included in the national treatment guidelines as a first-line therapy and in the Thailand Essential Medicines List. These inclusions resulted in establishing a predictable level of demand for TDF-containing products; this has incentivized generics manufacturers to register TDF products in Thailand. Thailand's strong universal access program for HIV and centralized medicines procurement system have made purchasing TDF efficient. The majority of patients and health care providers perceive generic TDF to be of good quality.

The importance of the VL program in Thailand decreased when Gilead's patent application for TDF combinations (e.g. TDF/emtricitabine) was withdrawn. It is unclear what role the previous issuing of a CL for two other ARVs played in Gilead's decisions to withdraw its patent application for TDF.

Thailand started domestic, government-subsidized production in 2013. Nowadays most of the TDF containing products used in the government HIV program are domestically produced. However, the domestically-produced TDF has not yet received WHO PQ and it is unclear if it will obtain WHO PQ in the near future given the technical requirements and the available funds.

In the case of sofosbuvir, Thailand had to threaten to issue CL before it was included in the Gilead VL program. To date, the GPO has not been included as a licensee and so imports the API for use in its production.

### Key Background Facts

| **NATIONAL HEALTH SYSTEM** | |
|---|---|
| Gross National Income per capita | US$ 18,160 |
| Total Health Expenditure per capita, 2009 | US$ 178[8] |
| Local pharmaceutical industry | Yes, including public manufacturing (Government Pharmaceutical Organization) |
| Percent of people living with HIV who are on ART | 72 [63 - 83][9] |
| Total AIDS annual expenditure, per capita PLWHA | 2009*: USD $415.2[10]<br>2018: USD$1,973.7 (1,564.3 to 2,446.3)[11] |
| **DISEASE BURDENS** | |

[8] http://files.unaids.org/en/media/unaids/contentassets/documents/data-and-analysis/tools/nasa/20140707/thailand_2008-2009_en.pdf
[9] https://www.unaids.org/en/regionscountries/countries/thailand
[10] http://files.unaids.org/en/media/unaids/contentassets/documents/data-and-analysis/tools/nasa/20140707/thailand_2008-2009_en.pdf
[11] Conflicting data: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30698-6.pdf

| | |
|---|---|
| HIV prevalence rate, adults 15-49 | 1.1 [0.9 - 1.2][12] |
| HCV prevalence rate | 0.94%[13] |
| **PATENT STATUS, LICENSING, AND REGISTRATION** | |
| Tenofovir monotherapy | Patent applications not filed[14] |
| Tenofovir/Emtricitabine 150/100 mg<br>Tenofovir/Emtricitabine 300/200 mg | Patent application: 12/01/2004[14]<br>*Withdrawn* [date of withdrawal unclear] |
| Tenofovir/Emtricitabine/Efavirenz 300/200/600 mg | Patent application: 12/01/2004[14]<br>*Withdrawn* [date of withdrawal unclear] |
| Sofosbuvir 400 mg | Filed [expected expiry date 28/04/2024] |
| Sofosbuvir+Daclatasvir 400+60 mg | Filed [expected expiry date 28/04/2024] |
| Sofosbuvir/ledipasvir 400/90 mg | Filed [expected expiry date 28/04/2024] |
| Sofosbuvir/Velpatasvir 400/100 mg | Filed [expected expiry date 28/04/2024] |
| Sofosbuvir/Velpatasvir/Voxilaprevir 400/100/100 mg | Filed [expected expiry date 28/04/2024] |
| Compulsory license for TDF | No |
| Compulsory license for SOF | No |
| Registration: Gilead's Viread (TDF) | Approved, 2006[15] |
| Registration: Generic TDF | Information pending |
| Registration: Gilead's Truvada (TDF/FTC) | Approved, 2008[16] |
| Registration: Generic TDF/FTC for prevention | Approved[17] |
| Registration: Bristol-Myers Squibb and Gilead's Atripla (efavirenz,emtricitabine, and tenofovir) | 2010[18] |

## Timeline of Key Events

**2001** Establishment of "30 baht scheme", the government universal health program

**2003** Government establishes policy of universal access to ARVs

**2006** **Thailand is included in Gilead's direct VL territories for TDF**

Establishment of government committee for compulsory licenses (CL never included TDF)

Government issues a compulsory license for efavirenz to the Government Pharmaceutical Organization (GPO)

United States Trade Representative (USTR) lists Thailand on its "Special 301" Report Watch List, citing weak protection for pharmaceutical test data and delays in pharmaceutical patent approvals

[12] https://www.unaids.org/en/regionscountries/countries/thailand
[13] https://apps.who.int/iris/bitstream/handle/10665/277005/WHO-CDS-HIV-18.46-eng.pdf?ua=1
[14] https://www.medspal.org/?keywords=tenofovir&country_name%5B%5D=Thailand&page=1
[15] https://khn.org/morning-breakout/dr00039498/
[16] https://www.prepwatch.org/country/thailand/
[17] https://www.prepwatch.org/country/thailand/
[18] Personal communication, Aaron Brinkerhoff

**2007** Government issues compulsory license for lopinavir/ritonavir, with plans to import it from Matrix in India[19]

GPO contracts with Ranbaxy to import 66,000 bottles of efavirenz

**2010** TDF as first-line treatment added to National Treatment Guidelines

**2011** **Thailand included in Gilead-MPP license for TDF**

**2013** GPO begins producing TDF

**2014** Gilead withdraws patent applications for TDF and combinations[20]

**2017** **Thailand included in Gilead's Voluntary Licensing Program for SOF**

## Key facilitators and barriers to make TDF available in the county

### 1. Patent status, licensing, and registration

*Facilitators:*

- Inclusion of Thailand in the VL program in 2006 allowed importation from India and domestic production

Thailand was included from the outset in 2006 in the TDF VL program. This made it possible for Thailand to use imports from Indian manufacturers that had direct licenses with Gilead. A substantial portion of the demand for TDF in Thailand was from the government HIV treatment program. After generic TDF products were made available via the government HIV program, demand for the originator product from Gilead remained from the private market.

Gilead's withdrawal of patent applications in Thailand then made domestic generic production possible, and advocacy within Thailand successfully promoted domestic production. According to one interviewee, advocacy by civil society organizations, including the Thai Network of People Living with HIV/AIDS (TNP+), led Gilead to withdraw its patent applications for several TDF-containing products in 2014.[21]

This action, combined with the Gilead giving permission to Indian licensees to sell API to the Thai Government Pharmaceutical Organization (GPO) made it possible for GPO to develop domestic production over the next two years. While Thailand had been eligible for VL since 2006, the patent withdrawal made TDF-containing products accessible without the need for a VL from Gilead. Domestic production provided Thailand with more independence from imports and Gilead's VL program.

- Streamlined product registration through use of multinational standards

Registration of TDF for the Thai market was facilitated by streamlined processes. The Thai FDA uses both ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines and ACTD (Association of Southeast Asian Nations (ASEAN) Common Technical Dossier)

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[19] Available at: Kaiser Health News. Available at: https://khn.org/morning-breakout/dr00043558/
[20] https://www.medspal.org/?keywords=tenofovir&country_name%5B%5D=Thailand&page=1
[21] https://www.medspal.org/?keywords=tenofovir&country_name%5B%5D=Thailand&page=1

procedures to register both imported and domestic medicines, facilitating timely registration. Using these processes, GPO gained approval and registration for tenofovir with emtricitabine for use in prevention (PREP); this represented a major success story for ARV access in Thailand.

More recently, the Thai FDA has begun considering WHO PQ as well, and on that basis has accepted an application for an HCV medicine that includes sofosbuvir fixed-dose combinations. Compatibility with PQ dossiers facilitates the registration process.

According to the GPO, in 2019 domestically-produced TDF combination therapy is the dominant therapy in the country. However, Thailand does have a full range of TDF options in the market, including Gilead-produced products, TDF produced by Indian manufacturers with bilateral licenses, and locally-produced TDF containing products from GPO.

*Barrier:*

- Resource-intensive processes for approval of domestic products

Despite advocacy to expand domestic production, GPO and the Thai government have limited resources to perform clinical research and bioequivalence studies. GPO began producing TDF in 2013, but did not get approval or registration from the Thai FDA until 2016 due to the burden of investing in studies.

Comparator: Sofosbuvir Access Program

*Facilitator of inclusion of Thailand into the VL program for sofosbuvir*

- Advocacy based on Malaysia's CL threats

Thailand was *not* included when Gilead initially launched the sofosbuvir access program in 2014. Thai treatment advocates pushed to get sofosbuvir for Thai patients; their efforts were eventually successful, after the Thai government threatened Gilead with a CL. Malaysia had already successfully gained entry to the VL program after issuing its own CL. Thailand then entered Gilead's VL program in 2017, three years after the program launch. Thailand has since obtained the medicine, sourced from the same Indian generic suppliers as are supplying to Malaysia.

*Barriers to domestic production of sofosbuvir:*

- Thailand's GPO is excluded from VL

While Thailand is included in the territory of Gilead's VL for sofosbuvir, the GPO has no direct bilateral license with Gilead. Rather, GPO can sign a sublicense with an Indian-based manufacturer. GPO representatives perceived that a lack of direct communication with Gilead as the reason for the delays and difficulties with the sofosbuvir product development process.

- Slow registration of generic sofosbuvir

The first generic sofosbuvir product was not registered until 2018. According to one interviewee, the delays in generic product registration stemmed from lack of clarity in the market registration dossier. A large dossier was required, including bioequivalency studies, setting a high standard to pass.

**2. Inclusion in the Essential Medicines List and treatment guidelines**

*Facilitator:*

- Commitment of the Ministry of Public Health and coordination among agencies

TDF was adopted for use in Thailand thanks to coordination among different agencies in the Thai health system. The prospective availability of affordable generic TDF encouraged the Ministry of Public Health to revise the national HIV treatment guidelines, which included TDF-based regimens as first-line treatment beginning in 2010.[22] In tandem, the National Health Security Office extended its health benefit package to cover TDF-based regimens. The National Essential Drug List Committee then took into consideration the National Treatment Guidelines, stakeholder consultations with clinicians and civil society, and a cost-effectiveness study. The cost-effectiveness study required manufacturers to submit a price, subject to negotiation before adoption. This process was decisive in getting TDF included in the country's EML. Negotiations on price began at this stage, and continued after inclusion in the list and at the procurement stage.

### 3. Domestic production, including quality assurance

*Facilitator:*

- Subsidies for production by Thai government

The Thai government decided to subsidize local production. It provided investments into GPO, to enable its transition from importing finished products from Indian manufacturers to producing formulations using the API from Indian manufacturers. Information provided by GPO shows that their product prices for TDF-based therapies are below those of Indian manufacturers in the majority of the domestic ARV market.

- Collaborations with Indian manufacturers

While GPO had received technology transfer support from Mylan to begin producing efavirenz, this assistance was apparently not made available for the production of TDF-containing products. Nonetheless, relationships with Indian manufacturers willing to export finished and unfinished materials into Thailand made TDF production possible. At present, GPO representatives report that they supply domestic TDF-based medicines to most of the country's market.

*Barriers:*

- Lack of direct relationship with Gilead

GPO representatives expressed a wish to have a one-to-one VL directly with Gilead that includes technology transfer. Interviewees stated that GPO had developed its TDF-based products essentially without outside help, and expressed a desire for technical assistance from Gilead which would have greatly helped with product development.

- Lack of expertise

GPO lacks the capacity to produce the API for TDF. GPO relies on imported API, which it uses to produce finished doses for domestic sale. This reliance on importation limits Thailand's potential to produce its own medicines.

Gilead representatives confirmed that the company was unwilling to license directly to domestic Thai manufacturers such as GPO, explaining that it would reduce market competition among the

[22] https://www.who.int/hiv/pub/guidelines/thailand_art.pdf

international generic manufacturers. “Handing the market” to the domestic manufacturer, they argued, passes the monopoly from the originator to the domestic producer without increasing access.

- Challenging to gain PQ

Prequalification would enable Thailand to export domestically-produced medicines to countries with stringent regulatory standards or to countries that depend on donor support; lack of PQ limits the potential market for its products. GPO representatives expressed that while they would like to apply for WHO PQ for tenofovir, the process is expensive, resource-intensive, and time-consuming. GPO did successfully receive WHO PQ for efavirenz in 2018,[23] an accomplishment that they credited to tech transfer from Mylan. GPO considers the achievement an indirect indication that their TDF would also be demonstrated to be of good quality. However, an official explained that GPO would undertake careful consideration before applying for PQ for another product. The bioequivalence studies, patient-reported outcomes, and other requirements of the PQ application process require major investments from the Thai health system.

Representatives of the WHO PQ program confirmed that the PQ process requires meeting high standards that are difficult for many smaller, less sophisticated manufacturers to meet. While WHO PQ has a technical support program aimed at helping small manufacturers pass and maintain its standards, GPO would be an unlikely participant because of its status as a state-run enterprise rather than a private business. GPO is a relatively long-standing and well-established pharmaceutical manufacturer in the region; its obstacles to PQ highlight that the WHO PQ mechanism may not be well-equipped to support the expansion of medicines access domestically.

- API supply chain problems

GPO representatives described facing difficulty in accessing high-quality API from Indian manufacturers, reporting problems with product stability and temperature conditions in shipping and storage. While minor compared to other barriers to domestic production, these issues show that GPO’s capacity to produce combination doses remains subject to the uncertain quality of Indian licensees.

### 4. Procurement

*Facilitator:*

- Universal coverage allows efficient procurement

Thailand has a well-functioning universal health system that guarantees access to ARV. This creates predictable demand for manufacturers, including Indian manufacturers exporting to Thailand. Central procurement of HIV medicines makes price negotiations and volume forecasts more efficient. The VL program allowed Thailand to use lower-priced generic TDF. Another interviewee stated that the VL program was critical to creating access to TDF-containing products in Thailand.

*Barrier:*

- Domestically-produced TDF containing products may not receive WHO PQ

[23] https://extranet.who.int/prequal/news/gpo%E2%80%99s-efavirenz-tablet-prequalified

Because HIV program in Thailand is largely funded domestically, the government can choose to procure ARV medicines that have not received WHO PQ and/or that are produced outside the Gilead-VL TDF agreement.

### 5. Clinical use and acceptability

*Facilitator:*

- Changing perceptions of generic medicines

Previously, people living with HIV in Thailand had a poor perception of generic medicines, thinking that they were substandard or falsified. The Thai FDA has had to prove its capacity to ensure the quality of all medicines. Nowadays, HIV patients are very knowledgeable in Thailand and perceive generic HIV medicines as safe.

*Barrier:*

- There is a private market for branded medicines, including by Gilead. Some physicians advocate branded products. There are also some people living with HIV who prefer American-branded medications over Indian products.

## ZAMBIA

### Overview

Zambia, which is categorized as a lower middle income country by the World Bank, has a generalized HIV epidemic with a prevalence of 11.5% in 2018. HIV is firmly established in the general population, and a high percentage (75%) of PLHIV are receiving antiretroviral therapy. As a result, Zambia's national HIV treatment program is of significant size. Since the national HIV program depend largely on donor funds, donors' requirements significantly influence decisions on procurement of HIV medicines (e.g. requiring WHO PQ of products). Because of its income status, the country is exempt from many patent protections until 2025.

Zambia was included in Gilead's initial VL program beginning in 2006. Zambia was an early adopter of generic TDF at a time when most other LMICs had not yet switched from the (more toxic) stavudine-based first-line regimen. Clinicians in Zambia advocated the use of TDF, regardless of whether the product was an originator or generic TDF. Donors supported the procurement of generic TDF by the national HIV program. Negotiations by CHAI with Aspen, which had signed a bilateral license with Gilead, were seen as instrumental in promoting the use of generic TDF, as were other conversations that Gilead facilitated between the Zambian Ministry of Health and Aspen.

### Key Background Facts

| **HEALTH SYSTEM** | |
|---|---|
| Gross National Income per capita | US$ 4,100 |
| Total Health Expenditure per capita, 2016 | US$ 56.54[24] |
| Local pharmaceutical industry | None relevant to either TDF or SOF production |
| Percent of people living with HIV who are on ART | 75 [70 - 81][25] |
| Total AIDS expenditure, per capita PLWHA | 2016: USD$347[26] |
| **DISEASE BURDEN** | |
| HIV prevalence rate, adults 15-49 | 11.5 [10.9 - 12.3][27] |
| HCV prevalence rate | 0.6%[28] |
| **PATENT STATUS, LICENSING, AND REGISTRATION** | |
| Patent status of TDF in country | No (LDC status exemption) |
| Patent status of SOF in country | No (LDC status exemption) |
| Compulsory license for TDF | No |
| Compulsory license for SOF | No |
| Registration: Gilead's Viread (TDF) | No[29] |
| Registration: Generic TDF | Yes |

[24] https://data.worldbank.org/indicator/SH.XPD.CHEX.PC.CD?locations=UA
[25] https://www.unaids.org/en/regionscountries/countries/zambia
[26] https://www.healthpolicyproject.com/pubs/7887/Zambia_HFP.pdf
[27] https://www.unaids.org/en/regionscountries/countries/zambia
[28] https://pdfs.semanticscholar.org/29fb/04f7f04566eb4c7687d8d7a3e3528dbce670.pdf (Look for better reference)
[29] https://www.who.int/selection_medicines/committees/expert/20/applications/Viread-submission_WHO-EML_Final_13-Mar-15.pdf

| | |
|---|---|
| Registration: Gilead's Truvada (TDF/FTC) | Approved |
| Registration: Generic versions of TDF/FTC for prevention | Approved[30] |
| Registration: Bristol-Myers Squibb and Gilead's Atripla | Approved[31] |

## Timeline of Key Events

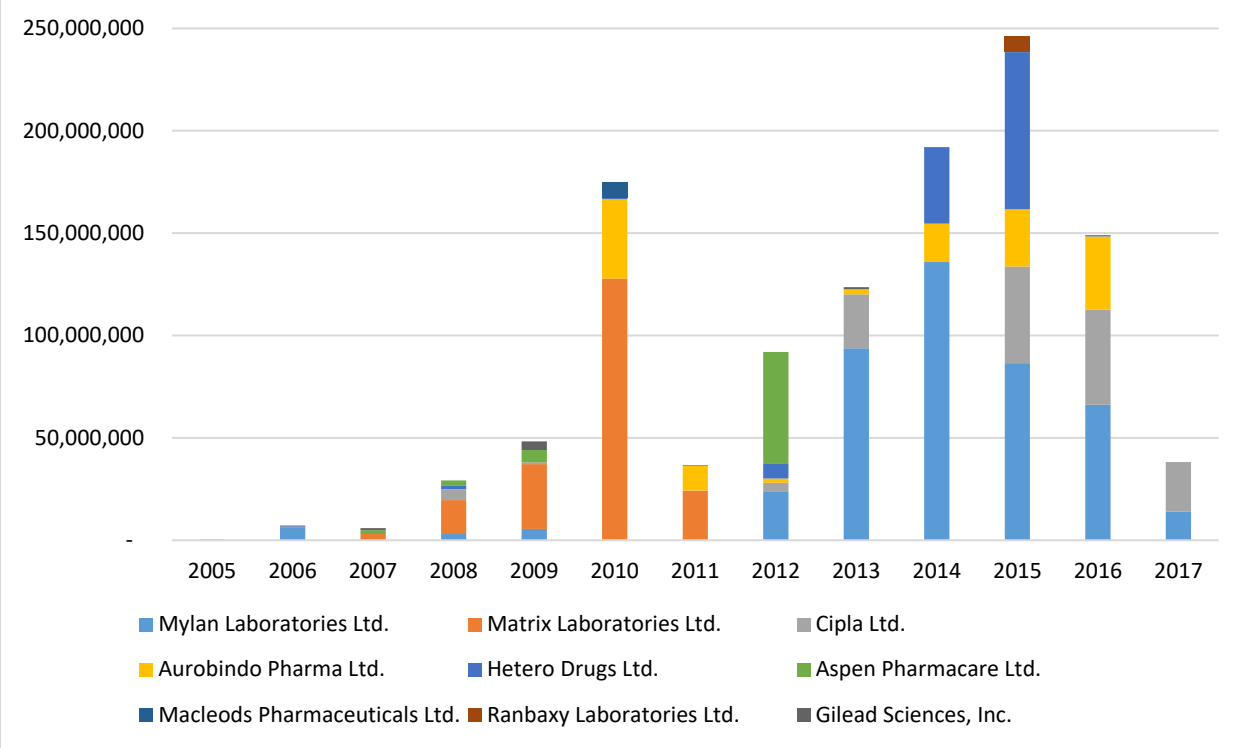
| | |
|---|---|
| 2006 | Zambia is included in direct Gilead VL for TDF |
| July 2007 | "Amid some donor controversy" TDF is introduced as part of first-line therapy. Zambia is the first African country to use TDF "on a wide scale."[32] |
| 2011 | Zambia is included in the MPP VL for TDF |
| 2013 | Generic Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) from Mylan introduced as first-line therapy in Zambia |
| 2015 | Zambia is included in direct Gilead VL for SOF |

**Note on procurement of generic TDF using donor funds**

As early as 2006, generic TDF was procured for import into Zambia. Figure 1 shows data from the Global Price Reporting Mechanism (GPRM). Given that Zambia's national HIV program depends largely on donor funds, the GPRM data should capture a large percentage of the total consumption of TDF-containing medicines. Mylan and Hetero were the dominant manufacturers of TDF containing products procured for import into Zambia (Matrix was acquired by Mylan). A very small amount of donor funds were used to procure Gilead products. Except for Cipla and Macleod Pharmaceuticals, all the generic manufacturers listed had either a bilateral or a MPP license for TDF.

[30] https://www.prepwatch.org/country/zambia/
[31] https://www.merck.com/corporate-responsibility/docs/access/atriplaregistrationstatus.pdf
[32] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2862003/

*Figure 2: Total Number of Tablets[33] of TDF-Containing Medicine Procured, by Manufacturer, by Year, in Zambia 2005-2017*




[33] Global Price Reporting Mechanism (GPRM) unit is in most cases a tablet

## Key facilitators and barriers to making TDF available in Zambia

### 1. Patent status, licensing, registration

*Facilitators:*

- Least Developed Country (LDC) status

As a UN-designated Least Developed Country, Zambia is allowed an extended transition period before it must comply with the WTO TRIPS agreement.[34] Exempt from issuing patents, the country may access any available medicines regardless of generic or originator status.

While these rights are established, interviewees commented that even LDCs like Zambia may face implicit pressure from the US (a major donor) and the WTO to buy originator medicines and to respect existing patents or licenses. One interviewee noted that "the US and the WTO were wielding a big stick, and they would come for you if you tried anything. But once VL became available, that wasn't needed…Gilead realized that they don't have to be a policeman, running around checking on people. [In addition, they could] still make money on the volume of sales."

- Originator-generic collaboration

Stakeholders at Gilead reported a reciprocal relationship in which the company provided generic licensees with the data they needed to register their medicines in each country. This may speed up the time from VL to availability.

*Barriers:*

- Delays in registration

While some interviewees mentioned Gilead's diligence and collaboration on registration (noted above), one interviewee identified delays in generic product registration throughout sub-Saharan Africa as a barrier to access. This source cited originator companies' failure to register, requirements that originator companies register before a generic can be registered, and lack of incentives to register in countries with small markets. This was described hypothetically: "If Gilead has not updated the registration in a country, then that could be a problem. Or maybe the originator has to register before the generic can register. Or companies don't feel motivated due to the cost of registering in a given country, versus the market demand. In HIV, the margins are thin for generic manufacturers." However, the requirement of originator registration before generic medicines registration was only cited as a barrier in a few countries, notably, South Africa and Thailand.

- Lack of political will

A stakeholder at Gilead cited lack of political will among various authorities for delays in registration. The source identified the need for cooperation among heads of state, WHO, donors, regulatory authorities, manufacturers, and other parties to facilitate and speed up registration of medications.

[34] https://www.wto.org/english/tratop_e/trips_e/ldc_e.htm

### 2. Production of TDF or TDF combination products, either originator or generic

*Barrier:*

- Lack of collaboration with originators

One interviewee called for originators to collaborate to create patented fixed-dose combinations (FDCs), such one that would combine Gilead's tenofovir alafenamide (TAF) with GSK's dolutegravir. Originators make combinations of their own medicines, but clinicians want more FDC options than those allowed within companies' portfolios. The creation of patented FDCs might speed the way for new generic FDCs in a model similar to the Medicine Patent Pool. One interviewee noted the challenges involved, asking, "Who would make that?"

### 3. Inclusion of TDF in national Essential Medicines Lists and treatment guidelines

*Facilitators:*

- *Stakeholder collaboration*

According to Gilead, the adoption of TDF in Zambia can be attributed to a multi-stakeholder effort: after WHO added TDF to the WHO Model List of Essential Medicines treatment guidelines in 2007, PEPFAR and the Global Fund made funding available, and then it was possible to make a demand forecast for the country.

*Barriers:*

- WHO resistance to high-price medicines

In the early 2000s, a Zambian Ministry of Health technical working group recommended putting all first-line patients on TDF. This decision met with resistance from WHO due to concerns that the price was too high and preferring to keep TDF for second-line treatment. WHO wanted to expand access using cheaper medicines. The working group persisted despite WHO pushback, confident that with greater purchasing volume, the price would go down.

### 4. Procurement

*Facilitators of generic TDF procurement:*

- Collaboration among Ministry of Health, UNITAID, and CHAI

Interviewees reported that Zambia was outstanding as the first country to commit to using TDF as the first-line treatment for the population.[35] The most important element was advocacy by Zambian healthcare providers and clinicians seeking the best treatment options. Commitments of funding from the Elizabeth Glaser Pediatric AIDS Foundation and involvement by CHAI were significant. CHAI engaged generics manufacturers to ramp up production; then, as one interviewee noted, "Botswana and South Africa got on board," building additional demand.

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[35] Atripla was approved by the US FDA on 7/12/2006. Retrieved 1/1/2020 from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021937TOC2.cfm

The Zambian MoH engaged with Gilead, which then engaged with Aspen. One interviewee stated, “A lot of people thought that Gilead had gone crazy. This was a good molecule. You had thrown the ball over the wall. Why would you do that, if you could be making huge money with that medicine?...Aspen did quite well supplying southern Africa. Availability of product was not an issue.” While some interviewees credited Aspen with initiating demand, Figure 1 shows Matrix/Mylan as the major contributor to generic TDF sales in the transition period.

UNITAID decided to use its buying power to help generics manufacturers foster demand and start producing more product. Their order of TDF for the entire country of Zambia “kick-started” widespread demand for generic TDF. PEPFAR and the Global Fund worked more slowly.

*Barriers*

- Extensive demand

One interviewee noted that Zambia faced a rough transition to TDF for first-line patients, describing how “the country suddenly had 100,000 patients in need of the same medicine.” Meanwhile, generics manufacturers were invited to a competitive tender process requiring each manufacturer to begin producing the medicine without knowing whether they would be able to sell it. This could have been avoided if an appropriate demand forecast had been done for the entire market beforehand.

- Donors’ resistance to generics

In the early 2000s, PEPFAR and the Zambian government were the main funders of ARV treatment in the country. While the Zambian government was committed to changing to generic TDF, but the US-supported PEPFAR was only buying branded products at the time. CHAI stepped in at that point to broke a deal with Aspen and other generic companies to begin producing generic TDF under Gilead’s VL, steadily taking over the Zambian market and driving down prices. In the same period, Indian generic companies reportedly began doing their own advocacy in the US to change the donor’s perceptions of generics. In the second half of the 2000s, PEPFAR policies changed and generics became the default.

### 5. Clinical use

*Facilitator*

- Clinical superiority of TDF

The Ministry of Health had a working group in charge of expanding access to ARVs. Tenofovir’s mutation pathway and toxicity were better than the older medicines in use in the country, stavudine and zidovudine. The working group determined that TDF was a better product for patients.

### 6. Patient use

*Barrier*

- Lack of patient education

One patient advocate saw major shortcomings in Gilead’s access campaign from the patient side, describing Gilead’s “major failure” to invest in patient education in Zambia (and similar countries receiving primarily generics). Concerns were raised that because profits are low, neither originator

companies are not motivated to educate people living with HIV about the clinical profiles of different products, nor do generic manufacturers invest in patient education. While there has been occasional financing by originator companies for this purpose, one interviewee expressed a wish that Gilead would set up a fund to educate patients in Africa, as Viiv Healthcare has done in some countries.[36] While governments and the public may receive general information, they explained, PLHIV need and deserve a deeper understanding of the medicines that they are taking, including details about marginal differences in toxicity, side effects, or dosages. This education could even address the clinical benefits of voluntary licensing. The interviewee stated, "The trick is that the knowledge [about VL] is only available through highly technical conferences and meetings, so it is not easy to learn about this. Gilead does not have a deliberate program to inform patients. Maybe in the US or other high-income countries, Gilead informs patients, but not in Africa. Here, patients get the same information as the general public and the government."

[36] Available at: https://viivhealthcare.com/en-gb/our-stories/advancing-hiv-treatment-and-care/addressing-the-challenges-of-the-hiv-epidemic-in-africa/

# ECUADOR

## Overview

Ecuador has a concentrated HIV epidemic, with a prevalence of less than 1% in the general population. The Ministerio de Salud Publica (MSP) treats approximately 70% of the country's HIV patients and is required to follow national treatment guidelines, meaning that adoption of a new regime can happen quickly but otherwise there is little demand for new medications. The national HIV program is largely domestically funded, so external donors have little influence over procurement.

In the case of TDF, its introduction to the country was slow and delayed. Demand for TDF was relatively small. Physicians used a wide variety of ARV combinations and had little incentive to streamline ARV treatment regimens. TDF was only included into the clinical practice guidelines in 2012 as a first-line treatment.

Gilead decided not to neither file patent applications of TDF in Ecuador nor to include Ecuador in its TDF Gilead Access program between 2006 and 2011. Neither did Ecuador have a significant domestic production of TDF. Most global generic TDF manufacturers were not permitted to import to Ecuador, as it was not included in the territories of the Gilead Access Program. Gilead eventually added Ecuador in 2011 as a territory to the Access Program.

Whether a 2009 decree allowing compulsory licensing of pharmaceuticals made by President Correa influenced this change in policy is unclear.

Patients in Ecuador reportedly perceive imported TDF form India to be higher quality compared to domestic products; however, domestic policies favoring local industry hampered procurement of generic TDF from Indian manufacturers until 2016. Since 2016, when efforts to promote the local pharmaceutical industry failed, the national HIV program uses mostly TDF imported from Indian manufacturers that previously had a bilateral TDF license. The PAHO strategic fund is facilitating procurement using Global Fund negotiated TDF price.

Gilead initially tried to sell TDF for HIV treatment in the country, but abandoned the effort, although Viread is registered for Hepatitis B treatment.[37]

## Key Background Facts

| **HEALTH SYSTEM** | |
|---|---|
| Gross national income (GNI) per capita | US$ 11,410 |
| Total Health Expenditure per capita, 2016 | US$ 504.78[38] |
| Local pharmaceutical industry | Yes—mostly imports, e.g. Eskegroup, Oxialfarm. |
| Percent of people living with HIV who are on ART, 2018 | 57 [38 - 93][39] |
| Total AIDS expenditure, per capita PLWHA, 2018* | US$ 1566.9 (1143.8 to 2146.7)[40] |

[37] https://www.who.int/selection_medicines/committees/expert/20/applications/Viread-submission_WHO-EML_Final_13-Mar-15.pdf

[38] https://data.worldbank.org/indicator/SH.XPD.CHEX.PC.CD?locations=UA

[39] https://www.unaids.org/en/regionscountries/countries/ecuador

[40] https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30698-6.pdf

| DISEASE BURDEN | |
|---|---|
| HIV prevalence rate, adults 15-49 | 0.3% [0.2 - 0.6][41] |
| HCV prevalence rate | 1.4%[42] |
| **PATENT STATUS, LICENSING, AND REGISTRATION** | |
| Patent status of TDF including TDF combination products in country | Not filed[43] |
| Patent status of SOF including SOF combination products in country | Filed for compositions of sofosbuvir—expected expiry date: 2032<br>Withdrawn for processes and intermediates[44] |
| Compulsory license for TDF | Compulsory license decree by President Rafael Correa but no CL declared for TDF |
| Compulsory license for SOF | Compulsory license decree by President Rafael Correa but no CL declared for SOF |
| Registration: Gilead's Viread (TDF) | For Hepatitis B only, 2012[45] |
| Registration: Generic TDF, either alone or in combination | Yes, since 2009[46] (in total 13 products registered in 2019) |
| Registration: Gilead's Truvada (TDF/FTC) | Yes, 2012[47] |
| Registration: Generic TDF/FTC | Yes, 2012[48] |
| Registration: Generic versions of TDF/FTC for prevention | Yes, registration currently valid for prevention as well as treatment (E3) |
| Registration: Bristol-Myers Squibb/Merck/Gilead Atripla (EFV/FDC/TDF) | Yes[49] |

## Timeline of Key Events

2002 Ecuador requested CL for zidovudine + lamivudine (conbivir) from GSK, leading to price reduction from $350 to $60/month[50]

2006 Ecuador *not* included in Gilead VL for Tenofovir

2009 Compulsory license decree by President Rafael Correa[51]

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[41] https://www.unaids.org/en/regionscountries/countries/ecuador
[42] https://www.sciencedirect.com/science/article/pii/S1198743X14616487
[43] https://www.medspal.org/?product_standardized_name%5B%5D=Tenofovir+300+mg&page=2
[44] https://www.medspal.org/?product_standardized_name%5B%5D=Sofosbuvir+400+mg&page=2
[45] https://www.who.int/selection_medicines/committees/expert/20/applications/Viread-submission_WHO-EML_Final_13-Mar-15.pdf
[46] http://permisosfuncionamiento.controlsanitario.gob.ec/consulta/index.php#
[47] https://www.gilead.com/~/media/files/pdfs/other/truvada_registration_022417.pdf
[48] https://s3.amazonaws.com/msd18-assets/wp-content/uploads/2019/06/13151941/ATRIPLA-Registration-Status-MSD-June-2019.pdf
[49] Source: ARCSA-REGISTROS SANITARIOS-ENTRICITABINA-TENOFOVIR
[50] https://www.ip-watch.org/2009/11/23/ecuador-to-define-its-compulsory-license-legislation/
[51] https://www.wipo.int/edocs/lexdocs/laws/en/ec/ec035en.pdf

| | |
|---|---|
| 2010 | Ecuadorian government issued a compulsory license for Eskegroup SA, a local distributor of Cipla, to import API for ritonavir, paying royalties to the originator, Abbott. Matrix/Mylan requested a compulsory license for ritonavir as well. [52] |
| 2011 | Ecuador included in MPP-Gilead license for TDF (Source: MPP-Gilead-Sciences-Amended-License) |
| 2012 | CL declared for abacavir/lamivudine and Kaletra (ritonavir + lopinavir).[53] |
| 2014 | Ecuador not included in Gilead VL for Sofosbuvir[54] |

## Key facilitators and barriers to make TDF available in the county

### 1. Patent status, licensing, and registration

*Facilitators:*

- Compulsory licensing decree created options

In 2009, President Rafael Correa issued decree No. 118[55], which states that the Ecuadorian government may issue compulsory licenses for any medicine in the public interest and emphasizing that "public health interests shall prevail over economic and commercial interests." In effect, Ecuador was not "obligated to respect provisions regarding the validity of patents," allowing the government to import or produce medicines from any source. The CL declaration made it possible for domestic laboratories to sell medicines to the public sector. However, the CL mechanism has not been used extensively and was not used for TDF. A few producers/importers are registered, but the volume of sale is low.

- Originator registration

*Registro Sanitario* with ARCSA (*Agencia Nacional de Regulación, Control y Vigilancia Sanitaria*) is necessary for a product to enter the market. Gilead initially tried to sell TDF for HIV treatment in the country, but abandoned the effort, although Viread is registered for Hepatitis B treatment.[56]

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[52] https://www.ip-watch.org/2010/04/22/ecuador-grants-first-compulsory-license-for-hivaids-drug/
[53] https://ihsmarkit.com/country-industry-forecasting.html?ID=1065991764
[54] https://www.gilead.com/-/media/files/pdfs/other/form%20ar%20hcv%20license%20agmt%20gild%2011202017.pdf?la=en
[55] http://oras-conhu.org/Data/201594141043.pdf
[56] https://www.who.int/selection_medicines/committees/expert/20/applications/Viread-submission_WHO-EML_Final_13-Mar-15.pdf

Comparator: Sofosbuvir Access Program

*Barrier*

- **Lack of clarity on patent status**

While sofosbuvir is patented in Ecuador, the country is excluded from Gilead's VL, limiting the country's options for obtaining the medicine. Gilead's velpatasvir/sofosbuvir for Hepatitis C patients with kidney failure is not available as a generic. At approximately $4,000 per originator-brand treatment from Gilead, the medicine is not affordable for the national health system. There is confusion within the MSP as to procurement options given current licensing and patent conditions.

### 2. Quality Assurance

*Facilitator:*

- PAHO's role promoting quality assurance

PAHO, which assesses the capacity of national regulatory authorities in the Latin America region, has designated eight regulatory authorities as regional reference authorities. This policy supports the procurement of quality-assured medicines: if a medicine is not pre-qualified but is registered by one of these eight regulatory authorities, PAHO's Strategic Fund is allowed to purchase it. Because Gilead licensees for sofosbuvir were not required to gain WHO PQ, countries have been slower to adopt the medicine. A PAHO representative commented, "In the case of sofosbuvir and Hepatitis C treatment, it was very clear the impact of not having a PQ medicine." Since WHO PQ TDF was imported, there was no quality concern similar to sofosbuvir.

*Barrier:*

- Lax domestic quality standards

Domestic production is not subject to equally rigorous quality standards as either imported generics or originator products. There have been allegations about the lower quality of domestic medicines but these have not been thoroughly investigated. However, interviewees did not specify whether these allegations concerned domestic TDF or sofosbuvir products.

### 3. Domestic production

*Facilitators:*

- Private sector cooperation

Eskegroup has been the key national importer of generic antiretrovirals. When the national health system had stock-outs, Eskegroup donated medicines.

- Failed launch of domestic pharmaceutical industry

Attempts by the Ecuadorian government to launch a state-run pharmaceutical industry in the 2000s failed, leaving the country with little capacity to meet their own needs for ARVs. One interviewee noted, "The pharmaceutical industry has not made much effort [in] the production of antiretrovirals...There was an attempt by the previous government to create a large pharmaceutical laboratory and research center…this initiative started and facilities were made, but at the end with the oil crisis and all that, they

ran out of money, abandoned all those initiatives. Then everything has been in standby, without officially being abandoned."

This situation has facilitated the country's increased reliance on Gilead's Access program. In the last five years Ecuador has relied largely on the WHO PQ imported TDF from Indian manufacturers.

### 4. Treatment guidelines

*Facilitators:*

- PAHO-supported updates to clinical practice guidelines (CPG)

Because national CPG did not initially include TDF, there was no pressure to adopt the medication and no interest in being part of Gilead's Access Program when it began in 2006. PAHO's *Tratamiento 2.0* initiative[57] starting in 2011 helped Ecuador modernize outdated clinical practice guidelines. A medicine must be included in the national clinical practice guidelines (CPG) to be purchased by the national health institutions (whether Ministerio de Salud Pública, Seguro Social, etc.). MSP treats approximately 70% of the country's HIV patients and is required to follow national treatment guidelines.. The country's clinical practice guidelines for HIV did not include TDF as part of first-line treatment until 2012 (in the fixed-dose formulations TDF+ FTC and TDF+FTC+EFV).[58]

Prior to 2016, national politics made it difficult to cooperate with PAHO Strategic Fund to procure ARVs. Before this, the country received a mix of Indian generics, originator medicine, and some domestic production. Relying little on TDF, the country for many years continued to use older regimens such as atazanavir and zidovudine.

*Barriers:*

- Slow to include PrEP

National CPG did not include pre-exposure prophylaxis (PrEP) until mid-2019, when it was updated to include TDF/FTC.[59] However, prior to this, TDF for PrEP was still possible because prescribers did not have to specify whether the indication was for prevention or treatment. Thus far, the NGO Kimirina is the only source of PrEP in the country; MSP has only just begun to consider providing it in the public sector. So far, it has not been necessary to re-register TDF for PrEP, but this may change.

Before 2019 the government had been unwilling to include tenofovir/emtricitabine for PrEP in the nation's essential medicine list (Cuadro Nacional de Medicamentos Básicos).[60] Kimirina and the Coalición advocated for it in hearings in 2019. There is still no treatment guideline (*normativa*) for Hepatitis C in Ecuador.

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[57] https://www.who.int/hiv/pub/arv/treatment2_flyer_es.pdf?ua=1
[58] https://siluetax.files.wordpress.com/2012/06/guia-de-atencion-integral-para-adultos-y-jovenes-con-vih-2012.pdf, page 36.
[59] https://www.salud.gob.ec/wp-content/uploads/2019/06/gpc_VIH_acuerdo_ministerial05-07-2019.pdf, page 16.
[60] https://apps.who.int/medicinedocs/documents/s21672es/s21672es.pdf

5. **Procurement**

*Facilitators:*

- Procurement facilitated by PAHO Strategic Fund

PAHO's Strategic Fund negotiates procurement prices for generic ARV medicines, including TDF, based on Global Fund standard prices. Prices are published in long-term agreements.[61] All participating countries receive generic ARVs at the same price. One interviewee noted that: "We concentrate the demand of different countries so we can organize the deliveries. So for the industry it's good because they have some sort of estimation of how they are going to proceed in terms of sending this medicine to the country. And also there is some difference in the payment, because we pay the provider in advance and it's good for them. They have the guarantee that they are going to receive on time and everything. And the country [has time] to pay us, and that also helps then support them in order to organize the sustainability of their programs."

- Transparency

Some interviewees believed that price transparency, in the absence of confidentiality clauses, allows countries to share their negotiated prices and negotiate for better deals. The Strategic Fund requires transparency even for national deals.

- Domestic purchasing as a back-up mechanism

The MSP has two purchasing mechanisms for ARVs: the PAHO Strategic Fund and the Servicio Nacional de Contratación Pública, the national purchasing system. The national system works as a backup for the PAHO purchasing system. Previously, around 2008-2010, the national system was used predominantly including for TDF, but it has not been used in recent years as PAHO attains better prices.

- Government preference for generics

The government is required to prioritize generic procurement over originator; this is one of the reasons why the MSP procures generic TDF. The public sector currently procures only a few originator ARVs, when no generic is available.

- Consolidated demand estimates

The national legal framework requires annual demand estimates for medicines for the public health sector, bringing together estimates from MSP, Seguro Social, and other public institutions. This makes it easier to coordinate the supply between PAHO and national purchasing mechanisms. There have not been major ARV stock-outs in recent years, including TDF.

*Barriers:*

- Originator opposition to pooled negotiation

A PAHO representative described how countries face difficulties when attempting to negotiate prices, such as for sofosbuvir-containing products, directly with Gilead or through PAHO Strategic Fund:

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[61] https://www.paho.org/hq/index.php?option=com_docman&view=download&alias=46901-antiretrovirals-valid-until-31-dec-2021&category_slug=product-list-references-prices-8778&Itemid=270&lang=en

"If the country wants to purchase through the Strategic Fund and this is a patent medicine, we invite…the patent owner to present a price based on a volume that we made within the region. If we have some other countries that also have patents and are interested in purchasing through the Fund, we can concentrate this volume in order to have a bigger demand for the industry. The point here is that Strategic Fund works with one price for all. So sometimes the industry wants to, and they can feel okay to present a price and work with the Strategic Fund. And sometimes they just consider that the differential price is their policy and they don't want to move in a single price way… The countries [that] have patents try to negotiate directly [with originator manufacturers]."

Mercosur and Associate States have tried to implement pooled negotiation on pharmaceutical prices, with mixed results. Gilead offered slightly lower prices for sofosbuvir, but it remains expensive.[62] With respect to sofosbuvir, Gilead approached countries with individual pricing offers rather than negotiating with the entire bloc. PAHO was allowed in negotiation meetings as an observer but was not allowed to participate.

- No affordable procurement for private sector

The private sector, including NGOs such as Fundación Kimirina, has few options when purchasing ARVs. Only the public sector has access to PAHO Strategic Fund purchasing. Lacking affordable options, Kimirina had to negotiate an agreement in which MSP donates antiretrovirals, including TDF, to their PrEP pilot program. Kimirina is working with an international organization, *Coalición Plus*, to be able to develop direct agreements with pharmaceutical companies like Gilead and local representatives to procure medicines affordably for programs in the NGO sector. They currently only have access to expensive generic medicines. Originator TDF treatment in the private sector can cost as much as $600/patient/month, which is not sustainable for most patients.

- Lack of competition in domestic market

When PAHO Strategic Fund purchasing is not an option, the Ministerio uses *subasta inversa*, a "reverse auction" system to receive and compare tenders from producers. For the last several years, domestic producers have won the tender. Only one provider was registered to sell in the public sector, so they got the entire purchase.

- Weak support from Global Fund

The Global Fund has played a very limited role in Ecuador in recent years. Global Fund support for ARV purchasing stopped around 2010 for a variety of reasons, mainly the change in Global Fund policies prioritizing funding for lower income countries. The national HIV program is largely domestically funded, and the government buys all medicines. In 2012 the Global Fund asked for an Adherence Plan for the country. The plan was developed in 2013-14 but never adopted by the MSP.

There was a reported lack of support and guidance from GF on product selection, as well as on human rights, fighting stigma, and strategic litigation. Currently some GF funding is received for training in key populations.

**6. Clinical use**

*Facilitator:*

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[62] http://www.rets.epsjv.fiocruz.br/en/news/mercosur-countries-create-negotiating-mechanism-procure-high-cost-medicines-paho-support

- Improvements in health system

The Ecuadorian health system is steadily improving its capacity and sophistication in treating HIV: "In Ecuador, the attempt is currently being made to correct failures, to have laboratory tests for treatment follow-up, such as viral load or [CD4 or CD8] monitoring, in a much more timely manner. There are still some delays, but the country is making quite significant efforts. Before, you had to wait up to 6 months to know what your viral load was and obviously therefore, then, the doctor had to continue attending patients, just blindly, without knowing what the reason was, whether the scheme you are prescribing… is working or not."

According to the interviewees, there is no pharmacovigilance system in place. Interviewees explained that they are not aware of any major clinical issues with the use of TDF, as compared to efavirenz or other medicines where the key informant knew of some cases of problems.

*Barriers:*

- Conservative institutions

In contrast with Zambia's early leadership in adopting new regimens, Ecuador "preferred to wait and see" how other countries did in adopting new regimens, rather than being "an early adopter." This was also because of a lack of local clinical research. Ecuador looks to Perú, Colombia, and the United States for data before making policy decisions. Until it had the results information it sought, the country continued using lamivudine, zidovudine, and efavirenz, which had good clinical indicators. "We didn't see the urgent need to change without much evidence." But when Ecuador finally adopted TDF, it did so with determination ("*con fuerza"*), getting 85% of patients onto the regimen within a short time.

- Lack of health system capacity

Interviewees reported that Ecuador lacks the capacity to do bioequivalency and bioavailability studies. So far there have been no complaints about the quality of medicines in the country; however, interviewees felt that adequate pharmacovigilance is lacking.

**7. Patient use**

*Facilitator:*

- Patient advocacy

Patients reportedly often question the quality of domestically produced ARVs, viewing Indian generics as having better quality. An interviewee at Kimirina described the knowledgeable and active patient body that advocates for access to medicines as well as clinical and laboratory services: "They demand and pressure to always have the latest medicine that is on the market, that is, the latest innovations....Whenever there is a medicine that is more fashionable, so to speak, there is always a lot of pressure from patients to bring that medicine here to the country....The complaint that patients have—rightly—on the subject of the drug is that, sometimes they do not have enough laboratory support to be able to substantiate or, failing that, be clearer if the scheme is working well or not it is working well."

*Barrier:*

- Failure to educate patients

The *Coalición Ecuatoriana de Personas Viviendo con el VIH* identifies the lack of patient education as a missed opportunity for better adherence and disease control: One interviewee noted: “Because if you don’t inform everyone of the [beneficial] effects of the medicine, of the unwanted effects, if you do not talk about adherence, lifestyle changes, medications use, I think it’s difficult. It's hard to convince people and tell them, well, you have to take this medicine, because they say it's good.”

## Lessons Learned and Future Steps

By all accounts, including those of the KIs interviewed for this project, Gilead's Access Program for TDF has made a significant contribution to global access to medicines in LMICs. By issuing voluntary licenses for TDF to generics manufacturers, the program enabled health systems to provide access to life-saving medicine for millions of people living with HIV. It also enabled Gilead to build strong relationships with the generics industry and generate positive press and goodwill among patients, advocates, providers and policy makers. The impact and wider potential of its VL model has been recognized, adopted and expanded in the global health space.

To create a market for generic versions of patented products containing TDF, VL, either through bi-lateral licenses administered by Gilead or through the VL MPP model, requires: (1) a known and constant demand for the generic medicine; (2) resources to pay for the medication; and (3) a supply of the product of the desired quality. Further, inclusion of the medication in WHO STGs, the WHO Model List of Essential Medicines and national treatment guidelines is important to ensuring the long-term demand that makes production by generics manufacturers efficient.

While the TDF program has been successful, however, its speed and level of success varied in different contexts. This evaluation found that Gilead's VL program was most effective under the following conditions:

- In countries with a high prevalence of the disease so that demand for treatment was broadly recognized by both public health and political stakeholders
- In countries where Ministry officials, health care professionals and patients were knowledgeable about the medication and its potential impact
- In countries with limited domestic production of pharmaceuticals so that importation of generically produced medication was already a standard approach
- When strong support from health care financiers, including both government and donor agencies, was in place
- Where political will existed to smooth regulatory and bureaucratic requirements in the introduction of new medications

For Gilead, the longstanding program of VL of TDF represents the first VL-for-access program. The company's sofosbuvir VL program can be considered as "VL version 2.0." Both programs offer important lessons to Gilead as it considers future access efforts.

The results of this evaluation uphold the argument that VL should remain a central feature of Gilead's access programming. As a strategy, VL offers significant benefits and few drawbacks for the company. But there are improvements that can be made, particularly regarding which countries should be made eligible for products created under VLs and considering when it is appropriate to do direct bilateral licenses and when working through the MPP is more effective. As the global context of medicines financing changes, including with increasing expectations of national funding of medicines, all access programs need to continuously adapt to these changing circumstances.

Further, while there is general agreement that VL has a positive impact, there is a great need for more, and more nuanced, research on the practice, its effects, and how and where it fits within the ecosystem of access to medicines strategies. For Gilead's Access Program, it is necessary to further examine how elements of program design affect the outcomes and impact of access strategies. For example, more focused research should be done on the optimal number of licenses to be issued and health outcomes

of patients receiving medicines via different strategies. Establishing standardized approaches to measuring the impact of the Access Program would support decision-making as Gilead goes about developing future programs. Understanding the impact of VL, in comparison with other access strategies, in different contexts will prove relevant not only for Gilead's existing access programs for TDF and sofosbuvir but also for other therapeutic products.

More broadly, this report presents the different views of various stakeholders on the implementation of alternative types of VL (namely, bilateral, MPP, or one originator with multiple generics companies). Comparing the implementation processes of manufacturer-led and MPP-led voluntary licenses—from the perspectives of the originator, the generics manufacturers and medicines access advocates—would allow future efforts to be tailored appropriately to a given context.

The three cases presented in this report show that it is possible to identify predictors of the impact of VL on access to medicines and pharmaceutical markets in LMICs, and that the strategy can be adapted to different contexts. The cases of Thailand and Ecuador demonstrate that it is relevant for policy makers and other stakeholders to understand the effects of VL on domestic production of pharmaceuticals in LMICs.

Furthermore, defining which roles in expanding access to medicines (from research and development to production and marketing through to patient education and outreach) are most effectively carried out by which stakeholders can increase efficiency of access programs such as the one by Gilead. Finally, this report demonstrates that transparent and collaborative research efforts among academic, industry, governmental and civil society stakeholders can work, and can promote access to essential medicines around the world.

## Appendix 1: Table of Studies Used in Literature Review

| Citation | Medicines, countries, companies with VL | Study design | Methods | Main outcome variable |
|---|---|---|---|---|
| Sim, J., & Hill, A. (2018). Is pricing of dolutegravir equitable? A comparative analysis of price and country income level in 52 countries. Journal of virus eradication, 4(4), 230-237 | Meds: DTG<br>Countries:<br>India<br>Uganda<br>Ukraine<br>Egypt<br>Uzbekistan<br>Cambodia<br>Armenia<br>South Africa | Cross-sectional comparison of published prices for 2 medicines | Lowest list prices of DTG were extracted from national drug price or reimbursement databases for 52 countries. Price was recorded as US$ per person-year (ppy). We compared the price of DTG to minimum costs of production and reduced prices of EFV. | Median price per patient per year (PPPY) |
| Assefa, Y., Hill, P. S., Ulikpan, A., & Williams, O. D. (2017). Access to medicines and hepatitis C in Africa: can tiered pricing and voluntary licensing assure universal access, health equity and fairness? Globalization and Health, 13(1), 73. https://doi.org/10.1186/s12992-017-0297-6 | Meds:<br>Sofosbuvir and Sofosbuvir/Ledipasvir<br>Company:<br>Gilead<br>Countries: Egypt, Ethiopia, Nigeria, Democratic Republic of Congo, Cameroon, Rwanda and South Africa | Modelling countries' ability to pay for meds | Prices taken from 2016 World Health Organization report. To approximate country health budgets,<br>"a number of available and widely accepted indices on country/individual income (e.g. Gross Domestic Product (GDP)), alongside total country expenditure on health." | Cost of 12-week treatment with generic vs. brand medicine.<br>Median annual income per capita and the annual health budget of countries. |
| Reed F. Beall, Amir Attaran, A method for understanding generic procurement of HIV medicines by developing | Abacavir (ABC), Efiravenz (EFV), Tenofovir (TDF), Tenofovir + emitricitabine | Cross-sectional empirical analysis across countries | Linking antiretroviral (ARV) patent data from a World Intellectual Property Organization patent study on the 2013 World Health Organization's (WHO) Model List of Essential Medicines to all | Units of medicines procured. Types of patent protections & flexibilities in place in countries. |

| Citation | Medicines, countries, companies with VL | Study design | Methods | Main outcome variable |
|---|---|---|---|---|
| countries with patent protection, *Social Science & Medicine*, Volume 185, 2017, Pages 118-126, ISSN 0277-9536, https://doi.org/10.1016/j.socscimed.2017.05.012. | (TDF+FTC), Tenofovir + emitricitabine + efiravenz (TDF+ETC+EFV), Zidovudine + lamivudine+nevirapine (ZDV+3TC+NVP) | | available matching procurement records in the WHO's Global Price Reporting Mechanism. Cross-reference with lists of legal flexibilities which facilitate generic access where patents have been granted to estimate plausible relevance. | |
| Hill, A. M., & Pozniak, A. L. (2016). How can we achieve universal access to low-cost treatment for HIV?. *Journal of virus eradication*, *2*(4), 193-197. | Meds: TDF | Cross-sectional empirical analysis | Assessed the ARV prices in low- and high-income countries | Price per person-year (PPPY) |
| Chatterjee, Kubo, & Pingali. (2015). The consumer welfare implications of governmental policies and firm strategy in markets for medicines. Journal of Health Economics, 44, 255-273. | Country: India<br>Meds: oral anti-diabetic medicines: sitagliptin, vildagliptin, and saxagliptin | Cross-sectional comparison of empirical data to 3 counterfactuals | Using aggregate market transaction data, we structurally estimate demand and supply and use the parameter estimates in our model to simulate consumer welfare under various counterfactual scenarios. | consumer surplus measured in rupees per patient per day |
| Walsh, N., Durier, N., Khwairakpam, G., Sohn, A. H., & Lo, Y. R. (2015). The hepatitis C treatment revolution: how to avoid Asia missing out. Journal of | Meds: sofosbuvir<br>Company: Gilead | Cross-sectional empirical | Printed prices were obtained from bottle labels. Market prices are based on community procurement costs in Northeast India. Prices in other locations and through other suppliers may differ. All prices are for one 28-pill | Availability and pricing per bottle of 28 pills of generic sofosbuvir from manufacturers in India. |

| Citation | Medicines, countries, companies with VL | Study design | Methods | Main outcome variable |
|---|---|---|---|---|
| virus eradication, 1(4), 272-5. | | | bottle and in approximate USD (1 USD=62 Indian Rupees). | |
| Juneja, S., Gupta, A., Moon, S., & Resch, S. (2017). Projected savings through public health voluntary licenses of HIV drugs negotiated by the Medicines Patent Pool (MPP). PLOS ONE, 12(5), e0177770. https://doi.org/10.1371/journal.pone.0177770 | ATV, LPV/r, RAL, RTV, TDF, TDF/FTC, COBI, EVG, DTG, TAF. | Modelling until 2028 based on empirical data through 2015. Counterfactual model of situation in which MPP does not exist. | Estimate the savings generated by licenses negotiated by the MPP for ARV medicines to treat HIV/AIDS in LMICs for the period 2010–2028 (by subtracting the price of ARV medications expected as a result of the MPP licenses from a counterfactual situation in which the MPP does not exist).<br>Generate a cost-benefit ratio–based on people living with HIV (PLHIVs) in any new countries which gain access to an ARV due to MPP licenses.<br>Price differential between originator's tiered price and generics price, within the period where that ARV is patented.<br>The model is based on actual savings generated by MPP licenses up until 2015 [17] and projected estimates of PLHIV accessing ART in LMICs in future, drawn from UNAIDS Fast Track report.<br>Estimate the number of potentially impacted PLHIV for a particular ARV in a given year based on the drug's market share in that year. | Money saved through MPP VL. Cost-benefit ratio. Price differential between originator's tiered price and generics price. Number of potentially impacted PLHIV. |
| Chaves, G. C., Hasenclever, L., Osorio-de-Castro, C. G., & Oliveira, M. A. (2016). | Med: atazanavir<br>Country: Brazil<br>Framework: Partnership for | Case study interrupted time series 2005-2013 | Analysis of the importance of atazanavir for HIV treatment and its share of the MoH budget for ARV, and comparison of the prices paid by the | Expenditures and costs of the treatment per year |

| Citation | Medicines, countries, companies with VL | Study design | Methods | Main outcome variable |
|---|---|---|---|---|
| Strategies for price reduction of HIV medicines under a monopoly situation in Brazil. *Revista de saude publica*, *49*, 86. | Productive Development Agreement Company: Bristol-Myers Squibb | | MoH with international reference prices. | compared to international prices |

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# Appendix 2: Interview Guides

**Interview guide 1: For representative from Gilead**

*Your role in Gilead's VL program*

1. Could you describe your role in the VL program at Gilead?

*Gilead's VL programs – scope, success and challenges*

2. How did Gilead decide on the scope and timing of roll-out of its VL programs?
3. What do you consider the success factors of the tenofovir (TDF) VL program?
4. How does Gilead measure the effect of the TDF VL program?
5. What were the greatest challenges of the VL program in general? Are there specific challenges that only apply to TDF or sofosbuvir?

*Gilead's relation with generic manufacturers*

6. Did Gilead approach the generic manufacturers to negotiate a TDF VL or was Gilead approached by them? Was this different from sofosbuvir?
7. Could you describe the technology transfer that took place between Gilead and the generic manufacturers for TDF and sofosbuvir?
8. What were the conditions of the licensing in case of TDF and sofosbuvir? Would it be possible to share a copy of the voluntary licensing with us?
9. Would you be able to share with us data on the quantity of sales of each of the generic manufacturers for TDF and sofosbuvir? Do you know to which markets their products were sold and when? Do you know why there was a variation in the quantities between generic manufacturers?
10. If you would negotiate TDF or sofobuvir VL again with manufacturers what would you change?

*Comparison of Gilead's VL with other access options, e.g. MPP*

11. From your perspective, what are the advantages for licensing tenofovir to the Medicine Patent Pool in comparison to VL program?
12. What are the disadvantages about the licensing to the MPP in comparison to VL program?
13. How would you like Gilead to strengthen its VL program in the future, both for TDF and sofosbuvir?

*Wrap-up*

14. Who else do you suggest to interview within Gilead for this project? Do you have any suggestion who to interview outside Gilead for this project?

*Thank you very much.*

**Interview guide 2: for Medicine Patent Pool representatives**

*Role in MPP and negotiation of TDF VL*

1. Could you describe your role in the Medicine Patent Pool?
2. What was your role in the negotiation of the Gilead licensing tenofovir (TDF)?

*Gilead's TDF VL*

3. What were the conditions of the licensing? Would it be possible to share a copy of the voluntary licensing with us?
4. What were the greatest challenges of negotiating the TDF?
5. How does the MMP measure the success of the licensing of TDF?
6. If you would negotiate VL again with manufacturers what would you change?

*Generic manufacturers' TDF VL*

7. What was your role in negotiating the licensing of TDF to manufacturers?
8. What were the conditions of the licensing to these manufacturers? Would it be possible to share a copy of the voluntary licenses?
9. If you would negotiate VL again with manufacturers what would you change?

*Comparison MPP with other access options*

10. From your perspective, what are the advantages for licensing tenofovir to the Medicine Patent Pool in comparison to VL program?
11. What are the disadvantages about the licensing to the MPP in comparison to VL program?
12. How would you like Gilead to strengthen its VL program in the future in particular with respect to sofosbuvir?

*Wrap-up*

13. Who else do you suggest to interview within the MPP for this project? Do you have any suggestion who to interview outside MPP for this project?

*Thank you very much.*

**Interview guide 3: for representatives of the Global Fund to Fight AIDS, Tuberculosis and Malaria and PEPFAR**

1. Could you tell me more about your role at the Global Fund/PEPFAR?
2. Gilead announced 2005 the tenofovir (TDF) Voluntary Licensing (VL) programs. What effect did it have on countries receiving Global Fund support?
3. What do you think were the biggest challenges rolling out the TDF VL program? How did the Global Fund address these challenges?
4. In 2011 Gilead licensed TDF to the MPP. What effect did it have on countries receiving Global Fund?
5. What do you think are the biggest challenges of the MPP license in comparison to Gilead's voluntary licensing program?
6. If hepatitis C would be included in the portfolio of the GF or PEPFAR would VL program would you like to see for sofosbuvir?
7. If you could make suggestions how to improve Gilead's VL program what would be your three key recommendations?

*Wrap-up*

8. Who else do you suggest to interview within GF/PEPFAR for this project? Do you have any suggestion who to interview outside GF/PEPFAR for this project?

*Thank you very much.*

**Interview guide 4: for generic TDF manufacturers**

*Your role in the company related to Gilead's VL*

1. Could you describe your role in your company and how it related to the TDF VL with Gilead?

*Company's VL with Gilead – scope*

2. Could you tell me more about the evolution of the TDF VL with Gilead? Was Gilead approaching your company? Was your company applying to Gilead for TDF VL?
3. Could you describe the technology transfer that took place between Gilead and the generic manufacturers for TDF?
4. What were the conditions of the licensing in case of TDF? Would it be possible to share a copy of the voluntary licensing with us?
5. Would you be able to share with us data on the quantity of sales for TDF? Do you know to which markets their products were sold and when?

*Success and challenges to the VL*

6. What do you consider the success factors of the TDF VL with Gilead?
7. How does your company measure the effects of the TDF VL with Gilead? Sales? Geographical scope? Market share?
8. What were the greatest challenges of the VL with Gilead?
9. If you would negotiate a VL for another product with Gilead again what would you change?

*Wrap-up*

10. Who else do you suggest to interview within your company for this project? Do you have any suggestion who to interview outside your company for this project?

*Thank you very much.*

**Interview guide 5: for country representatives of HIV/AIDS programs**

*Your role in the country's HIV/AIDS program*

1. Could you tell me more about your role in the country's HIV/AIDS program?

*Effect of TDF produced under VL on the country's HIV/AIDS program*

2. Gilead announced 2005 the tenofovir (TDF) Voluntary Licensing (VL) programs. What effect did it have on your country's HIV/AIDS program?
3. What do you think were the biggest challenges in making use of TDF produced by generic manufacturers? Probe: registration, treatment guidelines, importation, procurement, supply chain.
4. In 2011 Gilead licensed TDF to the MPP. What effect did it have on your country/s HIV/AIDS program?
5. What differences, if any, does it make for your HIV/AIDS program whether TDF is produced under Gilead VL program or the MPP license?

*Hepatitis C program*

6. If hepatitis C would be included in the portfolio of the GF or PEPFAR would it make a difference to your country's Hep C program?
7. If you could make suggestions how to improve Gilead's VL program what would be your three key recommendations?

*Wrap-up*

8. Who else do you suggest to interview within the HIV/AIDS program? Do you have any suggestion who to interview within the country?

*Thank you very much.*

**Interview guide 6: for experts in VL**

*Your expertise in VL*

1. Could you tell me about your research in the area of VL?
2. Could you share with the any references that you think are particularly relevant to Gilead's voluntary licensing program, either TDF or sofosbuvir?

*Gilead's VL program*

3. What do you think has been the success of Gilead's VL program?
4. What do you think are the biggest challenges?
5. If you could make suggestions how to improve Gilead's VL program what were your key recommendations?

*MPP licensing versus Gilead's VL program*

6. What are the advantages of the MPP VL compared with Gilead's licensing?

## Appendix 3: Table of activities, output, outcomes and factors affecting the Gilead's TDF Access Program

| Step | Type | Description | Main actors involved | Factors influencing Gilead's TDF Access Program |
|---|---|---|---|---|
| 1 | Activity | Patent application filing of TDF in specific low or middle income countries | Gilead | -Interest in market monopoly of TDF for the time of the patent protection |
| 2 | Activity | Offer of bilateral voluntary license to one or more manufacturers | Gilead | -Interested in offering license to certain territories in which Gilead does not have infrastructure to market TDF |
| 3 | Activity | Technology transfer from the originator to the generic manufacturer | Gilead | -Generic manufacturers do not require (or require little) technology transfer |
| 4 | Activity | Registration of the product in countries where generic manufacturer sells product | Gilead | -Interest in market either for originator or for allowing generic TDF manufacturer to register using Gilead's clinical data |
| 5 | Output | Gilead signs license with manufacturer | Generic manufacturer Gilead | -Manufacturers with the technical capacity to produce TDF<br><br>-Manufacturers are already supplier of API<br><br>-Manufacturers and Gilead are interested in building a business relationship |
| 6 | Outcome | Production of the generic TDF | Generic manufacturer | -Demand for HIV medicines (number of people affected)<br>-Donor funding |
| 7 | Outcome | Quality assurance of the generic product | Generic manufacturer | - Requirement of WHO prequalification for Gilead's license |
| 8 | Outcome | Registration/market authorization of the generic product | Generic manufacturer | -Gilead registering products in countries<br>-Generics preparing technical dossiers and applying for country approval |
| 9 | Outcome | Pricing of the generic product in a given market | Generic manufacturer | -Cost of producing generic TDF market forces and government policies |
| 10 | Outcome | Inclusion in standard treatment guidelines | WHO Countries | -Superior efficacy and safety than existing option (stavudine) |

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|---|---|---|---|---|
| | | (international and national) | | -Price of TDF -<br>-Clinicians and civil society promoting inclusion of TDF in national guidelines |
| 11 | Outcome | Procurement & Distribution | Countries<br>Donors<br>Clinicians<br>Patients | -Health systems structure<br>-HIV national program structure<br>-Government and donor funding |
| 12 | Outcome | Clinical use* | Countries | -Provider knowledge & preference of product |
| 13 | Outcome | Patient perception* | Medical providers | -Quality concerns<br>-Misinformation<br>-Lack of patient education<br>-Provider preference<br>-Originator and generic company involvement in patient education |

*These aspects will be described in each country study