New Treatments for Hepatitis C Virus:

Strategies for Achieving Universal Access

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March 2014

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ACKNOWLEDGMENTS

I specifically would like to warmly thank Chloé Forette and Karyn Kaplan for their support and inestimable work on this paper.
For her great editing and comments: Andrea Benzacar.
And for all their invaluable comments, edits, and discussion: Kajal Bhardwaj, Cécile Cadu, Eric Fleutelot, Marcela Cristina Fogaça Vieira, Caroline Izambert, Gaëlle Krikorian, Priti Radhakrishnan, and Arthur Vuattoux.
I would like to address special warm thanks to Françoise Barré-Sinoussi, Tracy Swan, Els Torreele, Olivier Rescaniere, Shiba Phurailatpam, and Jennifer Ho.
And Sylvie Allouf, Tahir Amin, Monique Baudequin, Paul Cawthorne, Lorena Di Giano, Sattara Hattirat, Myriam Kirstetter, Laura Martelli, Othman Mellouk, Francisco Neves Da Silva, Sibylla Péron, Christine Stegling, and Sarah Zaidi.
And finally: Médecins du Monde, ACT UP-Basel and the International Treatment Preparedness Coalition.

ACRONYMS AND ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
ATV: atazanavir
BMS: Bristol-Myers Squibb
BRICS: Brazil, Russia, India, China, and South Africa
CL: Compulsory license
DAA: Direct-acting antiviral
ddI: didanosine
DNP+: Delhi Network of Positive People
EFV: efavirenz
EMA: European Medicines Agency
EML: Essential Medicines List
EVG: elvitegravir
FDA: Food and Drug Administration (United States)
FDC: Fixed-dose combination
GAVI: GAVI Alliance
GFATM: Global Fund to Fight AIDS, Tuberculosis and Malaria
GNI: Gross National Income
HCV: Hepatitis C virus
HIC: High-income country
HIV: Human Immunodeficiency Virus
I-MAK: Initiative for Medicines, Access & Knowledge
INP+: Indian Network for People Living with HIV/AIDS
IP: Intellectual property
IPO: Indian Patent Office
ITPC: International Treatment Preparedness Coalition
LDC: Least developed country
LIC: Low-income country
LMIC: Lower middle-income country
MdM: Médecins du Monde
MIC: Middle-income country
MPP: Medicines Patent Pool
MSF: Médecins Sans Frontières
PEG-IFN: Peg-interferon (pegylated interferon)
PLF: Projet de loi de finance de la sécurité sociale (France)
TDF: tenofovir
TNP+: Thai Network of People Living with HIV/AIDS
TPP: Trans-Pacific Partnership
TRIPS: Trade-Related Aspects of Intellectual Property Rights
TTAG: Thai AIDS Treatment Action Group
UNDP: United Nations Development Programme
USD: United States dollars
VL: Voluntary license
WHO: World Health Organization
WTO: World Trade Organization

EXECUTIVE SUMMARY

Background: the HCV pandemic

185 million people across the world are infected with HCV; 150 million are chronically infected. The HCV pandemic is concentrated in middle-income countries (MICs); while 15% of the 150 million people with chronic HCV live in high-income countries (HICs), 72% live in MICs and 13% in low-income countries (LICs). It is estimated that HCV-related liver complications kill 350,000 people annually. Currently, the standard of care is injectable peg-interferon (PEG-IFN) used in combination with ribavirin (RBV). The cure rate is 50-75%, and the treatment is associated with strong side effects. Worldwide, only a tiny percentage of people with HCV have access to treatment.

2014, a turning-point in the history of the pandemic

New treatments recently approved or soon to be authorized will offer a range of advantages compared with their predecessors: multigenotypic activity, fewer side effects, and higher cure rates, including for those in advanced stages of infection.

These direct-acting antiretrovirals (DAAs), are bringing with them great hope for millions of people, as their use may lead to excellent cure rates. Gilead's new nucleotide polymerase inhibitor/DAA sofosbuvir (SOF) was approved by the EMA in November 2013 and by United States FDA in December 2013. The cure rate with SOF is close to 90% according to recent clinical trials results. Janssen's simeprevir also received FDA approval in November 2013. Bristol-Myers Squibb (BMS) has submitted daclatasvir to the FDA. SOF will be most likely be followed by other DAAs marketed by AbbVie, Janssen, and BMS before the end of 2014.

The issue of access

Although these new molecules will improve the quality of life of people with HCV and increase the number of people cured, their price will be out of reach of most of the people who need it. Gilead, like the other firms, is planning to apply different marketing strategies: "standard prices" in HICs, "tiered pricing" in MICs, and voluntary licencing in LICs. This analysis, using epidemiological data specific to HCV, tries to determine whether the strategies employed by pharmaceutical companies would be good for access.

While experts estimate that the production cost of SOF is USD68-136 (per person for 12 weeks), in HIC, SOF is sold USD1,000 per pill or USD80,000-90,000 per person for 12 weeks in the United States - where it is estimated that 5,367,834 persons live with HCV. As a comparison, the median household income in the country is USD51,017 per year, and while it is estimated that 48 million of Americans do not have any health insurance. In France, the cost of SOF is set at USD905 per pill (USD76,000 per person for 12 weeks). According to calculations made on InVs/ANRS epidemiological data, to provide SOF to 55 percent of the 232,196 people affected by chronic HCV in France and who need treatment rapidly, it would be equivalent to the budget of the Assistance Publique des Hôpitaux de Paris for 2014 or 4 times what France has paid into the GFATM since 2001. In MICs, Gilead plans to sell SOF for at least USD2,000 (for a 12-week course). In Egypt, at a minimum price of USD2,000, the cost of SOF alone for 100% of people with HCV would represent fivetimes the country's total 2011 public health expenditures. In Indonesia, it would little bit more than the total annual health budget in 2011. More generally, at the prices set by pharmaceutical companies, universal access would be practically unachievable, even in countries who have strongly committed to access to HCV care, such as Georgia, Thailand and Egypt.

During the first HCV World Community Advisory Board (CAB) that took place between February 22 and 25 2014 in Bangkok, Gilead gave more precisions on the scope of the SOF voluntary license and the countries covered. Excluding the most affected countries in terms of number of people with HCV, this license is failing to address the issue of access to SOF in LICs & MICs. Theoretically, this license leaves out 77,4 millions people with HCV from the access in LICs and MICs. But, does the license give any guarantee to provide to the 57,1 millions other covered by the scope of the license a real access to treatment? Given the fact that there is no Global Fund on HCV to purchase treatments, diagnostics, and monitoring for LICs & MICs, there are really little chance that countries such as DRC or Cameroon, who are covered in the scope of the license, will start treating people with sofosbuvir anytime soon. Given its very limited scope, the Gilead's 60 countries voluntary license on SOF brings out the fact that its main objective is not to provide access to the people living in the countries included in the territory but to bind generic producers, mostly based in India, to prevent them to supply any excluded MICs (including China, Brazil, Thailand, Egypt, Indonesia, etc.). As for the other VLs signed in the case of HIV and projections made based on details of the HCV pandemic, they also fail to provide an appropriate answer to the HCV pandemic in LICs and MICs. Voluntary licensing will thus fail to respond to the HCV pandemic in the most affected countries and hinder the generic drug competition.

Learning the lessons from the fight against HIV/AIDS

If none of these strategies (standard pricing, tiered pricing, and voluntary licensing) are good in terms of access, what other possibilities exist? In the case of HIV/AIDS, the use of TRIPS flexibilities has shown great results for opening access and reducing drug prices. In India, the opposition and revocation of abusive patents have increased the competition and considerably helped to drive down drugs' prices. In countries such as Thailand and Brazil, the use of compulsory licensing in the case of HIV/AIDS has led to a substantial drop of the price of medicines.

INTRODUCTION

"We are witnessing a revolution in the treatment of hepatitis C virus with powerful molecules capable of curing the infection. There is no question that these treatments that can save millions of lives must be made universally available at an affordable price."

Pr. Françoise Barré-Sinoussi, 2008 Nobel Laureate in Medicine

The hepatitis C virus (HCV) was first discovered in 1989. In July 2013, the World Health Organization (WHO) estimated that over 150 million people are chronically infected worldwide.[1] If left untreated, the chronic form of this disease can cause fibrosis, liver cancer, and, in 20–30 percent of cases, cirrhosis.[2] The annual number of deaths due to HCV is estimated at 350,000 globally, or nearly 1,000 per day. However, this pandemic is far from receiving the proper attention it deserves from the international community. While, for the threat of pandemics such as bird flu in 2006 or the H1N1 virus in 2008 and 2009 (17,000 deaths), the WHO deployed major resources as precautionary measures, including stepping up the number of high-level meetings, it has to date not taken the steps expected to deal with the HCV pandemic. Although few and far between, epidemiological studies nevertheless show that no country has been spared. The HCV pandemic is concentrated in middle-income countries (MICs); while 15% of the 150 million people with chronic HCV live in High income countries (HICs), 72% live in middle-income countries (MICs) and 13% in low-income countries (LICs).

As we move into 2014, new treatments are coming to market. The promising results of recent clinical trials suggest that new treatments, called direct-acting antivirals (DAAs), should gradually take the place of the current standard of care: pegylated interferon (peg-interferon, or PEG-IFN) and ribavirin (plus a protease inhibitor, either boceprevir or telaprevir, for genotype 1). New treatments recently approved such as sofosbuvir or soon to be authorized will offer a range of advantages compared with their predecessors: pangenotypic activity, fewer side effects, and higher cure rates, including for those in advanced stages of infection.

It is hard to estimate the proportion of people worldwide who require immediate treatment, because an estimated 84% of the population in lower-middle-income countries (LMICs) and 96% of the population in LICs live in areas where initial testing is not accessible.[3] The HCV diagnosis rate in most HICs remains below 50% and is estimated to be less than 10% in most low- and lower-middle-income countries.[4,5,6] Diagnostic technologies are rendered inaccessible by their high price, and this, along with the high price of drugs, make governments reluctant to lead broad testing campaigns. In addition, there is a dearth of equipment, in particular in low-income countries, that are necessary to provide appropriate care for people with HCV, including hepatitis C RNA testing, HCV genotyping, and Fibrocan.

Most people who have tested positive for HCV antibodies are often symptomatic, in an advanced stage of infection, or already receiving care as they are coinfected with other diseases such as HIV/AIDS or another form of hepatitis. They often require treatment immediately. The epidemiological data currently available still fail to clearly establish the distribution of people with HCV at different stages of the disease (F0, F1, F2, F3, F4). The current guidelines vary from country to country regarding at what stage it is better to initiate therapy.

In addition, several countries witnessed an increase in incidence of HCV infection in the past half-century and anticipate an increase in HCV-related liver disease in upcoming decades.

Over the past decade, the lack of real and wide spread competition for the older treatment and the lack of testing and epidemiological data explain why only a tiny minority of people in the world have been able to access it so far despite an urgent need.

Thus, the arrival of DAAs is a major turning point in the history of this epidemic and a source of immense hope for people with chronic HCV to such an extent that in recent years a significant proportion of people in high-income HICs are delaying treatment initiation, awaiting the arrival of new drugs. Demand for new treatments might therefore be substantial in 2014 in HICs. However, there is no certainty that these new treatments will be made accessible to everyone everywhere, particularly in countries with the highest burden of disease, where the "soon-to-be-obsolete treatment" has been already out of people's reach for a decade. Moreover, the fact that 72 percent of people with HCV live in middle-income countries (MICs)raises specific concerns about funding for and access to new treatments.

This article examines various possible strategies for gaining and expanding access to new HCV treatments, and compares them in order to determine which approach might be most beneficial to the greatest number of people. In the case of HIV/AIDS, the introduction of robust competition from generic drug producers enabled large numbers of people to gain access to treatment, particularly in developing countries. We will explore how companies establish drug prices, and whether it is in the interest of people with HCV for their governments to accept these prices rather than to use generic versions of the drugs. With regard to voluntary licenses, we will examine the scope of license defined by Gilead for its new HCV treatment and its consequences and impact on access, as well as, more generally, the other voluntary licenses by Gilead, Bristol-Myers Squibb (BMS), and Janssen on HIV/AIDS with projections applied to the epidemiological landscape of the HCV pandemic, to see what proportion of people would benefit from these voluntary licenses in the case of HCV. Finally, we will examine the advantage gained through exercising flexibilities provided in the World Trade Organization's (WTO's) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS),[7] including through patent opposition and compulsory licensing.

METHODOLOGY

• The classification of countries into different regions is taken from the World Bank, as are life expectancy data and country rank based on economic status.[8]

• The epidemiological data used for each country are taken from Evolving Epidemiology of Hepatitis C Virus, by Daniel Lavanchy.[9] More recent figures may exist for certain countries, but the aim of this study is primarily to give an idea of the proportion of people who need access to HCV treatment. It is difficult to determine how many people with chronic HCV need to be put on treatment immediately; however, based on the forecasts made in this study, the proportion of people included and excluded in the geographic areas covered by voluntary licenses (VLs) would remain unchanged. While more recent figures denoting the number of people living with HCV in certain countries may be available, Lavanchy's November 2010 study is the only one to offer cross-country data on people living with chronic HCV.

• It has to be noted that the epidemiological data taken from the Lavanchy's report for France is different from the data hold by InVS (French Institute for public health surveillance). When used, data from InVS will be specified as such.

• For the chart on "Egypt's health public expenditures 2011 Vs. universal access to SOF", data related to level of fibrosis distribution have been extrapolated from a study presented by Professor Wahid Doss (Dean, National Hepatology Institute, Cairo Professor of Hepatology, Cairo University Head, National Committee for Viral Hepatitis) out of 2659 persons at the El fatemia Hospita, March 2012, MSF-TAG-OSF HCV 2012 , Paris, october 2012.

• Chronic HCV denotes an HCV infection of more than six months from seroconversion, where the body fails to eliminate the virus naturally as occurs in 15–40 percent of cases. This term therefore refers to an HCV infection once it has become chronic.

• For the VLs, analysis are based on both the scope of the license on sofosbuvir presented by Gilead during the 1st Hepatitis C Virus (HCV) World Community Advisory Board (CAB) that took place in Bangkok on February 22-25 2014, and forecasts based on models of license granted since 2001 by the pharmaceutical laboratories of Gilead, Janssen, and BMS, for their HIV/AIDS drugs, tenofovir (TDF) and emtricitabine/Quad, darunavir, and didanosine and atazanavir, respectively.

• The data for the geographic scope of VLs issued by BMS and Janssen laboratories for their HIV/AIDS drugs was derived from annex 3 ("Spotlight on Voluntary Licenses") of the Médecins Sans Frontières (MSF) 2013 report, Untangling the Web of Antiretroviral Price Reductions.[10]

• The data for the geographic scope of VLs issued by Gilead as part of the Medicines Patent Pool (MPP) are available in the license agreement of July 2011.[11]

• The estimates of the real cost to produce new drugs against hepatitis C are taken from the study, What Is the Minimum Cost per Person to Cure HCV?, by Andrew Hill and Saye Khoo, Department of Pharmacology and Therapeutics, Liverpool University, UK; Bryony Simmons, MetaVirology Ltd, London, UK; and Nathan Ford, University of Cape Town, South Africa.[12]

• The calculations done for the cost of sofosbuvir marketed by Gilead in France are taken from press articles and the social security financing Act for 2014,[13] as well as from the website of the Assistance Publique-Hôpitaux de Paris (AP-HP) http://www.aphp.fr/.

• Data on the quality of patents are taken from technical work and analysis carried out by a team of lawyers and pharmaco-scientists for I-MAK (the Initiative for Medicines, Access & Knowledge), an organization of lawyers, researchers, and scientists working on the patent system and access to treatment (http://www.i-mak.org/about-i-mak-mission/).

• The calculations made from local currencies to US Dollars were made between November 2013 and March 2014 based on the US Dollar exchange rate during this period compared to other currencies (http://www.xe.com/en/currencyconverter/) such as the Euro (EUR), the Thai Baht (THB), Indonesian Rupiah (IDR), the British Pound (GBP), the Egyptian Pound (EGP) and the Swiss Franc (CHF).

DISCUSSION POINTS

ACCESSING PEG-INTERFERON/ RIBAVIRIN DUAL THERAPY

Peg-interferon and ribavirin (PEG-IFN/RBV) is to date the most widely used treatment for chronic HCV infection. PEG-IFN is derived from biotechnology and based on a weekly injection of pegylated interferon; interferon is a glycoprotein produced naturally by the immune system. Ribavirin is a chemical pill. This dual-therapy treatment is known for its potentially serious side effects and toxicity. Its efficacy can depend on the virus genotype and other host and viral factors. Between 50 and 80 percent of people achieve sustained virologic response, or SVR, depending on their genotype. SVR means than HCV is undetectable six months after the end of treatment. The results of clinical trials on new drugs are promising and lead to hope that, in time, PEG-IFN will no longer be needed in the treatment of HCV. However, these studies have limitations, as they are not representative of all categories of people who need treatment, nor all the genotypes, including 4, 5 and 6 that are underrepresented in the trials. The excellent results of many the new treatments being studied need to be confirmed outside of the clinical trial context, in real-world situations. Until new DAAs are proved safe and effective and can replace the current standard of care, PEG-IFN continues to be an essential treatment.

HCV genotype by region

Region	Predominant HCV Genotype
Europe, North America, Japan	Genotype 1a, 1b (genotypes 2 & 3 are less common)
Southeast Asia	Genotype 3
Egypt, the Middle East, Central Africa	Genotype 4
South Africa	Genotype 5
Asia	Genotype 6

in *Guide to hepatitis C for people living with HIV. New York: Treatment Action Group; 2009 October.*

In addition to it's being complicated to use, PEG-IFN, as a biotechnology derived from living organism, is also more complicated to produce. Thus, Roche and Schering Plough/ Merck that hold the patent for PEG-IFN have not until now been worried about wide-scale competition from biosimilars, given the impossibility for any manufacturer to replicate the exact same product as the originator, but only being able to produce a "similar" product with "similar" effects and efficiency. The lack of an international regulatory system on biosimilars, and subsequent limited availability of alternative versions of PEG-IFN, has prompted many governments and humanitarian organizations to primarily follow the U.S. Food and Drug Agency (FDA) and the European Medicines Agency (EMA) requirements on biosimilar products and use those produced by Merck and Roche.

Therefore, although the Roche patent on PEG-IFN alfa-2a was revoked in India in November 2012 due to its lack of innovation, there is no real competition from the biosimilar market, and so the two firms can divide up the monopoly of a huge global market, keeping high prices in most places and sometimes opening negotiations to drop the price in countries where a serious competition appears as a threat, such as Egypt.

Egypt has made the greatest advances in developing a broad HCV access-to-care program and use a biosimilar of PEG-IFN that is produced by a local firm

Currently, access to PEG-IFN and ribavirin is far from optimal. The high cost of the drugs keeps them out of reach for the vast majority of people in need worldwide with price ranging from under USD2,000 in Egypt to almost USD20,000 in France and the US for a 48-week treatment course. The arrival of new therapies offers high hopes not only of better treatment, but also of breaking Roche and Merck's joint monopoly—though based on recent DAA approvals, their exorbitantly high prices may only compound the access problem.

DOCUMENTING TREATMENT NEEDS AMONG PEOPLE WHO INJECT DRUGS

The route of transmission makes HCV the most common viral infection among people who inject drugs (PWID), who are disproportionately affected. Of the 16 million PWID worldwide, an estimated 10 million are infected with HCV (67%). Globally, around 90% of new hepatitis C infections are attributed to injection drug use, but there is a continuing reluctance from a majority of governments and health institutions to provide treatment to PWID: only 2-4 percent of them are currently receiving treatment.

On October 2012, Médecins du Monde conducted a study in Georgia with the aim of generating new and additional evidence regarding the HCV epidemic among active PWID in Tbilisi, and highlighting the need to include this specific population in future HCV treatment programs.[14] Among the diagnostics, genotyping was performed and liver fibrosis was assessed. Of the 216 active PWID in the survey, 91.9% had HCV antibodies and 82.0% had a current infection. The proportion of severe liver fibrosis with HCV was high among PWID: almost a quarter (24.2%) needed treatment urgently.

POLITICAL WILL REGARDING ACCESS TO PEG-IFN: THE EXAMPLES OF EGYPT, THAILAND, AND GEORGIA

Egypt has made the greatest advances in developing a broad HCV access-to-care program. The country has decided to use a biosimilar version of PEG-IFN that is produced by a local firm, Minapharm Pharmaceuticals. Egypt's capacity for local production has resulted in Merck and Roche's significantly reducing the price of its PEG-IFN in Egypt to align with that of the Minapharm product to more than 250,000 people with HCV in Egypt (currently to about EGP 20,000 (USD2,872) through the Health Insurance Organization, affiliated with the Ministry of Health, or at government expense. In other countries, access to PEG-IFN/RBV varies, and the drugs often must be purchased out of pocket by individuals. In general, Egypt is the "developing" country with the most comprehensive PEG-IFN access program, though other countries, such as Thailand and Georgia, have also committed to universal access to treatment.

Over the past years in Thailand, for instance, according to Karyn Kaplan, "civil-society groups have pressured the government to address Thailand's unchecked HCV epidemic, demanding that PEG-IFN be added to the National Essential Medicines List (EML). Through community organizing and education, policymaker lobbying meetings, and direct actions, Thai AIDS Treatment Action Group (TTAG), the Thai Network of People Living with HIV/AIDS (TNP+), and others, secured a government commitment to expand HCV treatment access through the national healthcare program. In August 2012, Thailand put PEG-IFN on its national EML."[15]

Paata Sabelashvili, from the Georgian Harm Reduction Network[16] clearly identifies the price of PEG-IFN as one of the key factors limiting access to this treatment in Georgia: "Most people cannot afford HCV treatment, nor can their governments. My government, like others in the Eastern European region, is launching a national treatment program, but astronomically high prices will limit it. How can governments and donors effectively address HCV if Pharma refuses to drop drug prices?"

Arrival of new DAAs

Several new DAAs have come to market, notably protease inhibitors and, more recently in the European, U.S., and Japanese markets, simeprevir (Janssen) and SOF (Gilead). Others, such as daclatasvir (BMS) are being developed and should come to market beginning in 2014. On December 6, 2013, the FDA granted marketing approval to one of the most promising drugs (due to its pangenotypic activity, low side-effect profile, etc.), SOF. Initially, it will be used with PEG-IFN/RBV or RBV, and eventually it may be used in combination with other oral DAAs. The combination of SOF and daclatasvir offers one of the most promising therapeutic options, but the lack of willingness by Gilead and BMS to work jointly on its development may delay the process of developing a fixed-dosed combination (FDC).

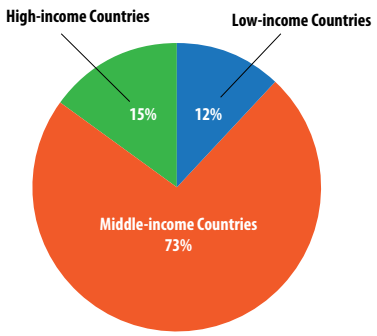
The preferred strategy of most pharmaceutical firms is to sign VLs allowing third-party manufacturers to supply LICs and to negotiate tiered pricing in MICs, as well as standard pricing in HICs

Although millions of people have been dreaming of the new treatments, with their better cure rates and lesser side effects, the therapy based on PEG-IFN and RBV is stillsaving lives and is the only option available in many countries.

ACCESS TO NEW DRUGS

The preferred strategy of most pharmaceutical firms (with the exception of a few laboratories such as Abbott/AbbVie)[17],is to sign VLs allowing third-party manufacturers to supply LICs and to negotiate tiered pricing in MICs, as well as standard pricing in HICs. In LICs and MICs that are badly affected by the HCV pandemic, what would a fair price be for DAAs? Is there such a thing as a fair price, and is the tiered-pricing approach proposed by the companies justified? What about VLs? Whom do they benefit? Will they really benefit anyone?

Distribution of people living with HCV in low-income countries, middle-income countries and high-income countries



The five countries with the highest concentrations of people living with HCV are China (29.7 million), India (18.2 million), Egypt (11.8 million)—which has the highest prevalence in the world (14 percent of the general population)[18]—Indonesia (9.43 million), and Pakistan (9.42 million).[19] The World Bank classifies all of these countries as middle-income countries (MICs). Of the 20 developing countries with the greatest numbers of people with HCV, 15 are MICs and five are low-income countries (LICs).[20]

Tiered pricing

Tiered pricing is the practice used by companies to offer different prices to each country, varying depending on the drugs, and very often with little transparency.[21] It might appear justifiable that the richest countries pay more for a drug than the poorest countries. However, on what criteria is the tiered pricing based? Is it based on the World Bank's ranking of countries, as is the case for the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and as would seem to be the case for voluntary licensing?

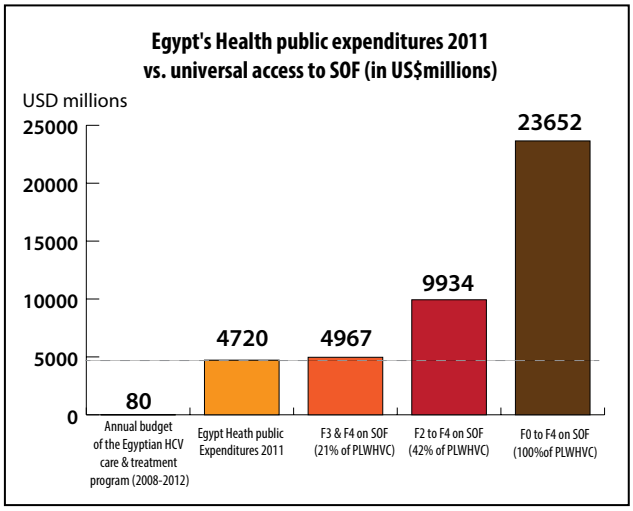
If so, and if we follow this line of reasoning, it would be logical for Botswana, classified by the World Bank as an upper middle-income country or even Nigeria, classified as a lower middle-income country (LMIC), and supposedly therefore richer than LICs, to pay higher prices than Kenya or Cambodia, which are considered low-income. But, is the World Bank classification any guarantee that the health services in Nigeria and Botswana are significantly better than those in Kenya and Cambodia? Can people living with HCV in Nigeria and Botswana afford these very high prices out-of-pocket? Certainly not. Can the governments of Nigeria and Botswana bear the burden of these prices? Probably not, given that life expectancy is 47 in Botswana and 52 in Nigeria—even lower than in Cambodia and Kenya.[22] Even if different factors explain the variations in life expectancy from one country to another, such as quality of life (environment, working conditions, situations of armed conflict or peace), access to basic health care is also a strong indicator.

To classify countries, the World Bank uses the gross national income (GNI) per capita criterion, with all the limitations this entails. This method of classification fails to take into account data such as the human development index; life expectancy; access to food, water, and healthcare; effectiveness or inadequacy of a national health insurance system; or even income disparities between the wealthier classes and poorer ones. Moreover, the limits defining these categories seem arbitrary and weak: countries whose per-capita GNI is USD1,035 or less are classified as LICs; those with a per-capita GNI over USD1,036 are considered MICs. Despite its obvious limitations, the World Bank classification has an enormous impact on the inhabitants of these countries, as it constitutes the basis for the arguments put forward by many international organizations[23] to justify the exclusion of some of them from development programs and access to care.

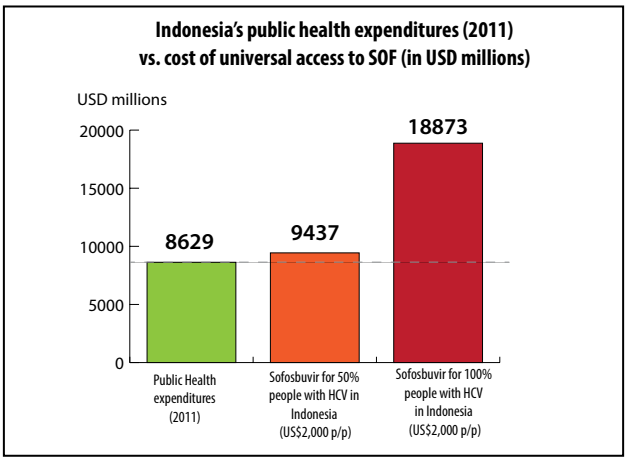
The examples of Egypt and Indonesia

Gilead will offer a range of prices for SOF starting at USD2,000, and increasing according to World Bank country classification, for a 12-week treatment course (not including the cost of RBV or PEG-IFN).

In Egypt, where close to 12 million people have HCV, at a minimum price of USD2,000, the cost of SOF alone for 100 percent of people with HCV would represent five times the country's total 2011 public health expenditures. Providing SOF (alone) to only those Egyptians at an advanced stage of the disease (F3 and F4)-and who need treatment urgently -would cost the government almost 62 times the entire annual budget of the Egyptian HCV care and treatment program (2008-2012). It reaches 124 times if Egyptians with a level of fibrosis F2 are included.



In Indonesia, where close to 9 million people are living with chronic hepatitis C, more than USD9,437 billion would be required, or a little bit more than the total annual health budget to provide SOF alone at a minimum price of USD2,000 to 50 percent of people with HCV.



Clearly, not all of these people need to be put on this treatment regimen, and many can wait to treat their HCV later (and therefore may have recourse to a drug other than SOF when the next DAAs come to market). Nevertheless, this projection is provided to demonstrate the exorbitant and unrealistic prices demanded by Gilead and the comparative burden such a pricing scheme would impose on health systems in low- and middle-income countries. This level of pricing also demonstrates that pharmaceutical companies are not trying to promote universal access to their drugs, but to maximize profits as quickly as possible. Even with a very strong political will, most governments cannot afford SOF at these prices for all who need it. Purchasing at the current price would require them to spend

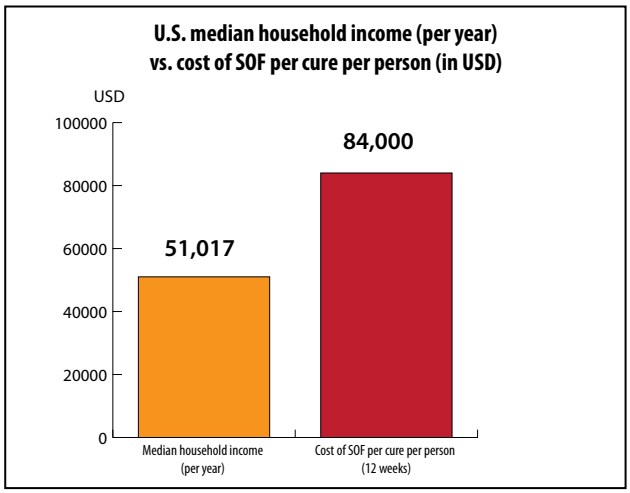
their entire annual public health budget, as if HCV was the only disease their health systems had to deal with. Even with strong political will and commitments from governments such as in Thailand and Georgia, universal access has not been possible to achieve, partly due to originator prices for PEG-IFN.

IS THE RICH/POOR CLASSIFICATION RELEVANT?

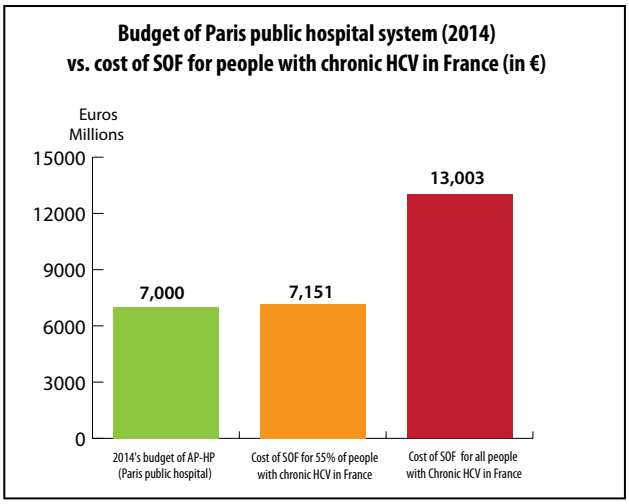
Suerie Moon, research director at the Harvard Global Health Institute, analyzes the current debates on the price of medicines in HICs and MICs the following way: "The rise of the MICs is challenging pre-existing arrangements in the development aid system, including the informal norm that "rich" countries pay higher prices for patented medicines to cover R&D costs, while "poor" countries purchase generics (at least for some priority diseases). But this rich/poor classification is neither as easy nor useful as it once was. MICs now include over 100 countries, home to over two-thirds of the world population, with 75% of the world's poor and a majority of the global burden of disease, with per capita incomes spanning from $2.84 to $33.56/day."

Standardized pricing, the examples of the United States and France

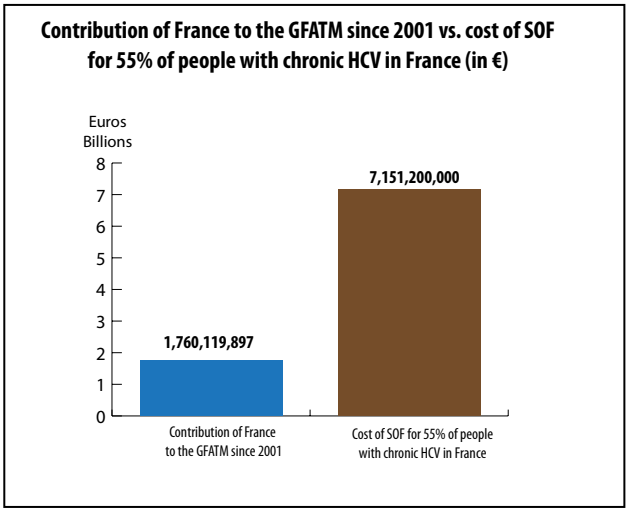
What about developed HICs, which represent close to 15 percent of the global epidemic? In the United States, Gilead charges USD1,000 per pill (€729), or USD84,000 (€61,288) for a 12-week course of treatment, which does not include the price of the other drugs, or of diagnostic and laboratory tests. In the United States, where the health insurance system is highly complex and reimbursement systems vary enormously from one insurance plan to the next, some of those requiring treatment—including the 48 million Americans who do not have any health insurance,[24] have to pay part of this sum out of pocket, and insurers have little leverage to negotiate lower prices. In the United States, a 12-week course of SOF costs more than the median household income (USD51,017 per year).[25]



In the United States, the power and influence of the pharmaceutical lobby, and the power of the pharmaceutical industry in the domestic economy, prevents any kind of transparent process on price negotiations or any kind of public debate. But recent studies have shown that generic drugs, which make up almost 80 percent of the medicine used, helped Americans save USD193 billion in 2011 as health care expenses rise and insurers force more consumers to use them.[26]



In France, where the health care system ensures that people do not have to assume any out-of-pocket expenses, Gilead has requested over €56,000 (USD76,751) from the Ministry of Health for SOF. So far, it has been impossible to obtain an official estimate of how much SOF the French government is planning to purchase from Gilead in 2014 and following years. However, the Haute Autorité de Santé is expected to provide more transparent figures in the upcoming months. People with a level of fibrosis from F2 to F4 and those with complications represent 55 percent of the 232,196 people affected by chronic HCV in France: that is 127,700 persons. If they were all put on a course of treatment that included SOF, the purchase of SOF alone would represent slightly more than the 2014 budget of the Paris public hospital system (Assistance Publique des Hôpitaux de Paris).[27]



Compared with the contribution of France to the GFTAM, the drug would cost public health insurance €7.15 billion (USD9.92 billion), or four times what France has paid into the GFATM since 2001 (€1.76 billion/USD2.41 billion)[28] to combat the three global pandemics over the past decade.[29]

Why does Gilead demand such an exorbitant price for its drug? Are the manufacturing costs so high? According to a study carried out by Andrew Hill, Saye Khoo, Bryony Simmons, and Nathan Ford,[30] based on its molecular structure and comparing it with Gilead's similarly structured HIV drug, tenofovir disoproxil fumarate (TDF), the production costs for SOF are estimated at €50–99 (USD68–USD136)—with an average of €74 (USD102)—or one-twentieth of the lowest price for SOF being offered by Gilead to MICs (USD2,000) for 12 weeks of treatment.

Predicted Minimum Costs of Hepatitis C Virus Direct-Acting Antivirals[30].

Agent	Daily Dose, mg	Overall Dose Per 12 wk, g	Estimated Cost per Gram, US$	Predicted Cost, USD
Ribavirin	1000–1200	84–101	0.29–0.41[a]	34–$48[b]
Daclatasvir	60	5	2–6	10–$30
Sofosbuvir	400	34	2–4	68–$136
Faldaprevir	120	10	$100–$210	100–$210
Simeprevir	150	13	10–21	130–$270

[a] Current range of active pharmaceutical ingredients cost per gram from 3 Chinese suppliers.
[b] Shows cost for 1000 mg daily dose; $41–$58 for 1200-mg daily dose of ribavirin; adjusted with a 40% markup for formulation.

More generally, their analysis suggests that production costs for 2- or 3-drug combinations of interferon-free HCV treatment (for a 12-week course) would be USD100–200, while price estimates for such combinations are close to USD150,000.

Thus, in France, the price charged by Gilead to the health service is 752.4 times higher than the estimated real cost of production of the drug. Gilead can of course cite the sums that it invested when it purchased Pharmasset for USD11 billion in 2011.[31] But should people and public health services have to pay for these investments? Given the prices at which Gilead would like to sell SOF in HICs, MICs and LICs, it will take a very short time for Gilead to turn a profit on its investment." And, even though the issue of reimbursing Gilead's investments is of little interest to most of the millions of people who need access to care, it is worth noting that the company has already regrouped its investments as its stock price has doubled in one year.[32] Recent press articles also highlight that Gilead CEO John C. Martin has become a billionaire "on the prospects of a powerful new hepatitis C drug [...], [and] has a net worth of $1.2 billion, according to the Bloomberg Billionaires Index.[33]

In France, the price charged by Gilead is 752.4 times higher than the estimated real cost of production of sofosbuvir

How are the tiered and standardized prices being set? They appear to be based more on maximizing rather than simply yielding profits (see box: Cost of Production vs. Prices). Unfortunately, it would seem that these unjustified prices have been accepted without objection by international donor and development institutions and United Nations (UN) agencies, as evidenced by recent discussions[34] within the board of the GFATM, which led to the creation of a committee (led by UNDP, UNITAID, UNAIDS, GAVI, UNICEF, and the World Bank) to support the use of tiered pricing in MICs for HIV/AIDS treatments.

COST OF PRODUCTION VS. PRICES

"Pharmaceutical companies purposely maintain a confusion between the cost and price of medicines, suggesting there is an underlying cost rationale to justify the very high prices they charge," says Els Torreele, director of the Open Society Foundations' Access to Essential Medicines Initiative. Cost in general refers to the amount paid to produce a good or service and the cost represents the sum of the value of the inputs in production, including raw materials, labor, capital, and enterprise. The price refers to the amount of money that consumers/buyers have to give up to acquire a good or service. "And price is an artificial construct that may or may not have any relation to the cost. The difference between both is the profit margin. And in the case of new HCV DAAs, the profit margin appears to be very high. For instance, the cost of production of simeprevir is estimated between USD130 and USD270 for 12 weeks, but Janssen sells it for more than USD66,000 in the United States. In this case, the profit margin is very high".

Voluntary Licenses

While the commercial strategy of standardized and tiered pricing seems arbitrary, unsustainable, and inefficient from the point of view of access to health, what about the voluntary licensing approach? In the case of universal access to new treatments for HCV, could voluntary licenses (VLs) prove useful and effective? What are the consequences for the countries within its scope and for those excluded?

Voluntary licensing allows the patent holder of an invention to grant a license to a third party to produce that invention in return for a payment of royalties. The terms of the license stipulate certain conditions, such as the amount of royalties to be paid, as well as the countries in which the producer is allowed to manufacture and market the licensed product. VLs fit in with commercial strategies developed by pharmaceutical companies to allow them to

GILEAD'S 60-COUNTRY VOLUNTARY LICENSE TERRITORY FOR SOFOSBUVIR

Not surprisingly, it appears that most of the countries included in the scope of the VL (the 11 exceptions out of 60 are: Cameroon, Fiji, Ghana, India, Maldives, Mongolia, Nigeria, Pakistan, Pacific Islands (Palau), Papua New Guinea, Tonga) are either LICs or non-LIC least-developed countries (LDCs). Unsurprisingly, India, home of most generics producers including those who could become sublicensees of the VL, is also included in the territory of the license. Excluded from the scope of this license are all the Eastern European and Central Asian countries, most Eastern and South Asian countries (including China), Latin America (including Brazil), North Africa and the Middle-East (including Egypt), and several sub-Saharan African countries such as South Africa, Botswana, Namibia, Angola, and the Democratic Republic of Congo (DRC).

The "Exception" of the Islands

Out of 60 countries included in the scope of the VL, 11 are small islands. The total estimated number of people living with HCV in these 11 countries is 158,347. These countries are: Fiji, Kiribati, Maldives, Nauru, Pacific Islands (Palau), Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, and Vanuatu.

It is not new for pharmaceutical companies to include small islands in order to increase the apparent scope of their VL. In the case of HIV/AIDS, the pacific island of Palau has often been added to such territories. In Palau, there are two people with HIV, both of whom are currently on antiretroviral therapy, while excluded countries such as Indonesia, Thailand, China, and Brazil are home to millions of people with HIV/AIDS.

Of course, people on these islands deserve the same right to health and medicines as those in any other country, and their size should not be an argument used to deny them this right; however, given the lack of epidemiological data in these countries, it is clear that pharmaceutical companies have been using them to hide the weak scope of their VLs.

The scope of the license was presented on a hard copy during the first WCab in Bangkok (22-25 February 2014). The full list of countries is the following : Afghanistan, Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Cambodia, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Djibouti, Eritrea, Ethiopia, Fiji, Ghana, Guinea, Guinea-Bissau, Haiti, India, Ivory Coast, Kiribati, Kenya, Laos, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mongolia, Mozambique, Myanmar, Nauru, Nepal, Niger, Nigeria, North Korea, Pakistan, Pacific Islands (Palau), Papua New Guinea, Rwanda, Samoa, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands Somalia, South Sudan, Sudan, The Gambia, Togo, Tonga, Tuvalu, Uganda, United Republic of Tanzania, Vanuatu, Zambia, and Zimbabwe.

continue to control the market for particular drugs. VLs, as opposed to compulsory licenses (CLs) (see below), are thus not based on TRIPS flexibilities but on commercial strategies. On the other hand, CLs, which are issued by governments, allow governments and generics producers to manufacture cheaper versions of still-patented drugs while acknowledging patent holders' rights.

An article appearing in the *Hindu Business Line* on February 3, 2014, outlined Gilead's strategy for the marketing of Solvadi/SOF in India: "'We are going to give license to Indian companies, so there will be Indian production of our hepatitis C product. We are in discussions right now. We hope to announce those in the next couple of months,' [said] Gregg H. Alton, Gilead's Executive Vice-President, Corporate and Medical Affairs.... Gilead's soon-to-be sealed deal will include royalty payments and cover about 60 low and middle-income countries, he said, adding details were discussed during their latest visit to India."[35]

This license leaves out 77.4 millions people with HCV from the access to sofosbuvir.

During the first HCV World Community Advisory Board (CAB) that took place February 22–25, 2014, in Bangkok, Gregg H. Alton gave more details on the scope of the VL and the countries covered. Excluding the most affected countries in terms of number of people with HCV, this license fails to address the issue of access to SOF in LICs and MICs (see box: Gilead's 60-Country Voluntary License Territory for Sofosbuvir).

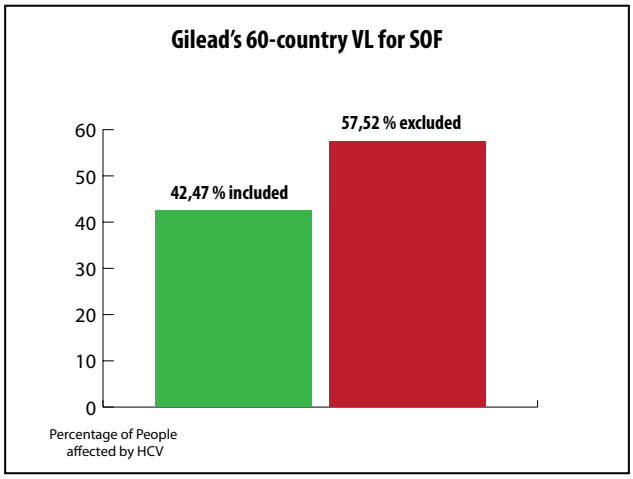
Theoretically, this license leaves out 77.4 million people with HCV from access to SOF in LICs and MICs. But does the license guarantee the 57.1 million others theoretically covered by the scope of the license real access to treatment? The VL does not provide this assurance to the people in these countries and also raises a range of unsettling questions.

Several countries with very high HCV burdens, such as Pakistan, Nigeria, and the DRC are included in the scope of the license, but how many people in these countries will benefit from it? A VL gives the right to a third-party producer to manufacture a product in a certain territory, but it does not mean that the price automatically drops and that the licensed drugs are provided for free. Given that there is no Global Fund on HCV to purchase treatments, diagnostics, and monitoring for LICs and MICs, there is little chance that countries such as the DRC where the most basic health facilities do not exist will start treating people with SOF in the upcoming months. Being in the scope of this VL does not ensure access to SOF for people in these countries, especially as it is also still unclear whether Gilead will register SOF or not.

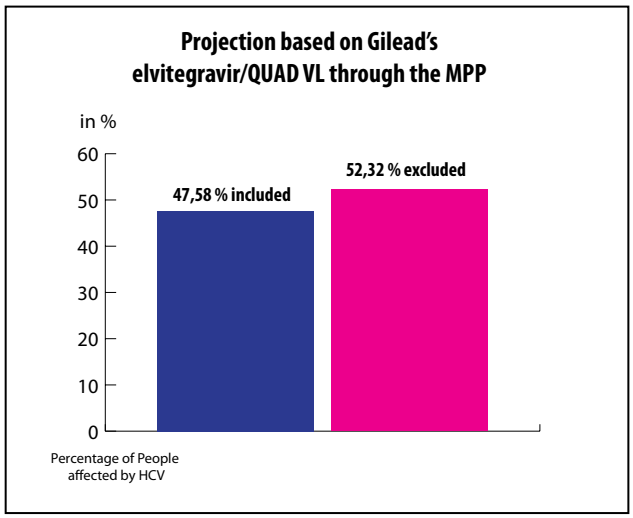
The registration of new DAAs in LICs and MICs is indeed also an issue, as originator companies might decide not to bother registering in countries where they do not see enough profits to be made, or where they fear strong generics competition. Not registering would spare companies administrative effort and at the same time prevent any generics manufacturers from registering a product in the country—even in a country covered by the VL.

What Would Voluntary Licenses for New Anti-HCV DAAs Look Like?

The licensing history of HIV/AIDS drugs provides a useful context for examining what VLs for new HCV antiretrovirals might look like.[36] However, Gilead's 60-country territory might already give a more precise idea of how future DAA VLs by BMS, Janssen or others might look like, as Gilead's SOF license will probably set the standard.

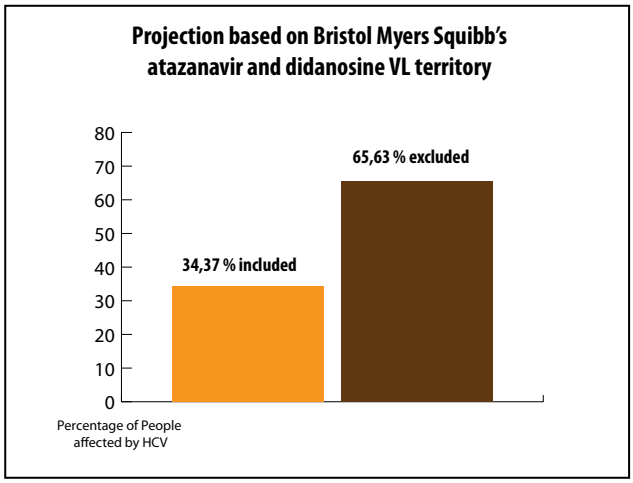


The Gilead license signed with the MPP for its EVG/QUAD combination, if applied to HCV epidemiological data, would provide access to SOF to only 47.58% of people affected by HCV and requiring treatment in developing countries.

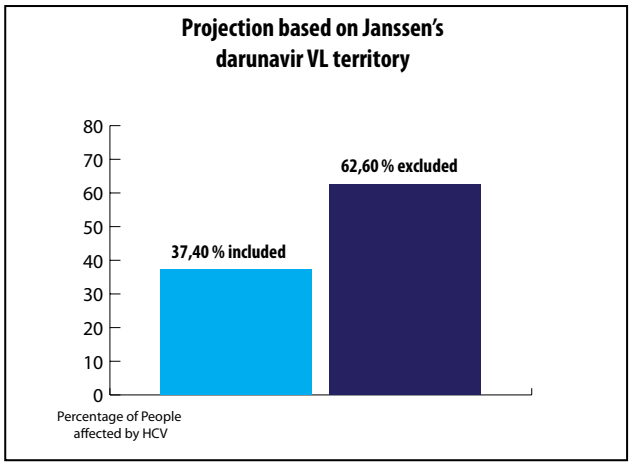


Voluntary licenses, as opposed to compulsory licenses, are thus not based on TRIPS flexibilities but on commercial strategies need.

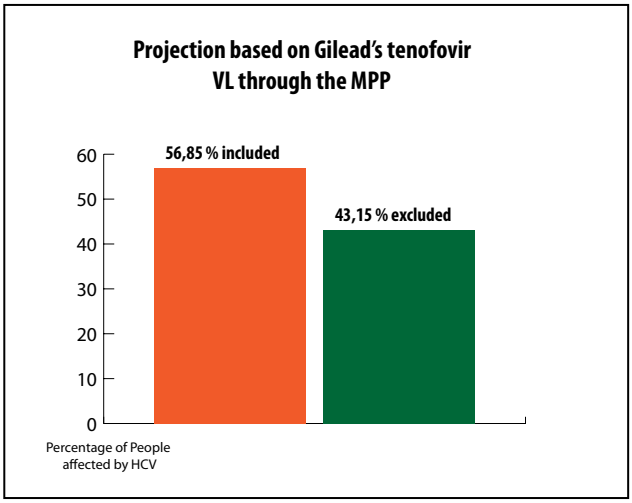
Since the early 2000s, BMS has always applied the same geographic scope for its VLs for atazanavir and didanosine (ddI). We can therefore imagine that this will also be the case for the new drugs it is currently developing. If we apply the same geographic scope as for the license for atazanavir (with Mylan in India) and ddI, only 34.37% of people requiring treatment for HCV in LICs and MICs would be in theory covered: 65.63% would be excluded in LICs and MICs.



Finally, if we apply the geographic scope of Janssen for its VL for darunavir, a third-line HIV drug, only 37.40% of people in LICs and MICs would be included.



The exception: Abbott/AbbVie: Abbott has always refused to negotiate voluntary VLs with generics producers. It is therefore impossible to include this company in the model, even though the complexity of its HCV combination might push the firm to change its strategy.[37]



Gilead, whose license for TDF was signed in 2011, has the widest geographic scope (112 countries). If the same area were used for SOF or another DAA developed by Gilead, only 56.85% of people who need the drug would have access to it in LICs and MICs.

To understand the broader territorial coverage of the Gilead/MPP TDF license, it is essential to recontextualize its signing in the framework of the first license negotiated between Gilead and the generic drug manufacturers in India in 2006, which included 96 countries.[38]

Patent oppositions

In 2006 in India, the INP+ (Indian Network for People Living with HIV/AIDS) and the DNP+ (Delhi Network of Positive People), with the support of a group of lawyers, filed an opposition to Gilead's patent on tenofovir. These groups of PLWHIV used legal remedies allowed under Indian law to challenge the validity of granting this patent based on India's patentability requirements. In September 2009, the Indian Patent Office (IPO) permanently revoked Gilead's patent for TDF.[39]

Regarding patentability requirements, each sovereign country has the right to amend its national patent law to suit its needs. If it is a member of the WTO, it must, however, comply with a certain number of rules, especially those under the TRIPS agreement, such as granting an exclusive 20-year right to all new patented inventions. On the other hand, the WTO grants countries a certain amount of latitude in terms of defining their patentability requirements. Thus, following India's accession to the WTO in 1995, section 3(d) of the Indian Patent Act of 1970 was amended to clearly define what is not patentable: all substances that are already known and are already protected by patents are excluded.[40] This clause is a safeguard against the practice of "evergreening," which involves pharmaceutical firms' applying for new patents for products that are only slight improvements on already existing ones so as to maintain a monopoly beyond the 20 years set out in the first patent.

India is the largest producer of generics in the world, and approximately 90 percent of drugs used to treat AIDS in LICs and MICs are produced there.[41] Revocation of the patent for TDF by the IPO presents a major risk for Gilead; the manufacturing of generic TDF by Indian companies (not as part of a voluntary license) would represent a significant market loss for Gilead, as many developing countries would likely prefer to get their TDF from a generics manufacturer rather than purchase it from Gilead at a much higher price. For instance, the price of TDF purchased from the originator firm Gilead in Russia is 21.2 times higher than the price of generic TDF in Brazil (USD700 in Brazil vs. USD3,300 in Russia)[42]. To maintain control over the market, Gilead decided to sign VLs with various generics manufacturers, covering 96 countries. These licenses provide Gilead with an advantage by binding the manufacturers to it. For these generics producers, the licenses provide the guarantee of a market, and spare them long and costly legal battles in Indian courts. While the validity of the TDF patent has been challenged in many countries (opposed in India in 2006, then in Brazil in 2011, and in China in 2013),[43] Gilead is nevertheless ensuring through these VLs that it obtains royalties in countries where it does not have a market monopoly.

Sofosbuvir is not innovative enough at the molecular level to warrant a patent

This example is even more significant as several legal and pharmacology organizations believe that the SOF patent has characteristics (including "weak" patentability) similar to that of TDF,[44] which barely met the patentability requirements set out in Indian law. On November 25, 2013, the organization I-MAK filed a patent opposition to SOF at the Kolkata Patent Office in India. "Sofosbuvir is not innovative enough at the molecular level to warrant a patent," said Els Torreele, director of the Open Society Foundations' Access to Essential Medicines Initiative.[44] In general, the issue of "strong" and "weak" patents raises a crucial question: is it lawful to pay royalties on a patented drug that did not deserve a patent because it is already "known" or has not been patented in a country?[45]

India's inclusion in the territory of VLs by originator companies is nothing new, as India is the home of most generic drug producers. It seems that VLs are mainly commercial efforts control manufacturing markets rather than a strategy based on truly expanding access to treatment to all those in need. This explains why India, despite its status as a MIC and a member of BRICS—the association of the five major emerging economies: Brazil, Russia, India, China, and South Africa—is consistently included in the pharmaceutical industry's VLs.

To conclude, it is clear that VLs do not offer many advantage for providing access to new HCV drugs, and may even prevent competition and access. Eighty-five percent of people with HCV live in MICs, unlike with HIV/AIDS, where the highest prevalence rates are in LICs in sub-Saharan African countries. For patents considered "weak," such as SOF, VLs are of most benefit to branded pharmaceutical companies to maintain influence over a huge market and keep control of a certain number of generics manufacturers. Cynically, we can even see VLs as a way for pharmaceutical companies to use the di-

SPOTLIGHT ON PATENT OPPOSITION AND "EVERGREENING"

In the case of HIV/AIDS, patent opposition has clearly shown results in terms of reducing the price of medicines and improving access to them. According to Marcela Cristina Fogaça Vieira, a lawyer at ABIA/GTPI, a working group on intellectual property coordinated by the Brazilian Interdisciplinary AIDS Association: "In Brazil, the patent application for tenofovir was rejected by the patent office in 2008 (and then again in 2009 and 2011), following oppositions filed by GTPI and Fiocruz. Since 2011, a Brazilian generic version of the medicine has been available, and the estimated savings are 47 percent in comparison with Gilead's price. This case shows very clearly how TRIPS flexibilities can be used to reduce the price of medicines and increase access."

Priti Radhakrishnan, co-founder and director of Treatment Access of I-MAK, on patent opposition and access to medicines: "One of the best features of a well-functioning patent system is the ability for any person to participate. Many countries permit third parties to present scientific and legal evidence when a patent office is deciding whether to grant a potential patent. The evidence may demonstrate that the potential patent is not a new invention or would have been obvious to someone working in the pharmaceutical industry, and therefore does not meet legal requirements to receive a patent. The final decision is always taken by the patent office, but it is a participatory and democratic feature of the patent system that the evidence submitted by third parties is taken into account. Oftentimes, third parties will choose to file this evidence, known as 'patent oppositions' in cases known as 'evergreening.' Evergreening refers to a practice of follow-on patenting, where applications will proliferate patent applications in an attempt to extend the life of their monopoly on a product, despite not meeting lawful requirements of inventiveness. If these applicants are successful, they can maintain their market monopoly for years and keep prices of essential medicines artificially high. If patent oppositions are successful, however, it curbs this practice of evergreening and allows low-cost alternative versions of the same medicine to become available at an earlier date, saving health systems billions of dollars and helping patients get access to affordable medicines."

vide-and-conquer strategy, between countries and people, those excluded and those included. For the few included countries where buying SOF generics will be possible and where the current HCV and health facilities will allow it, it is not even certain that any patent on SOF will have been granted, which would raise the question of Gilead's receiving royalties in countries where the firm does not have any exclusive right.

The strategy of opposing patents therefore is a relevant option, especially in the case of SOF, which is both effective and legal in countries where the national law allows it, as it helps to extend access to generics in all countries that do not fall in the geographic scope of VLs (as is the case for the majority of MICs). In countries where patents have been granted and cannot be opposed, and for molecules that are considered as real therapeutic novelty, a compulsory license could prove an appropriate option to provide access.

A VOLUNTARY LICENSE, WITH THE MAIN GOAL OF CONTROLLING THE GENERICS MARKET?

Given its very limited scope, Gilead's 60-country voluntary license for SOF reveals that its main objective is not to provide access to people living in the countries included in the territory—especially as it is unclear whether Gilead plans to register SOF or not. The main objective of this VL is to bind generics producers, most of them in India, in order to prevent them from supplying any excluded MIC. It seems clear that Gilead has already anticipated that governments of MICs would work to find alternative solutions to Gilead's out-of-reach-price for SOF, such as generic formulations, in order to provide access to the people of their countries. In attempting to kill any future generics competition, Gilead is already strengthening its monopoly on SOF.

Compulsory licenses

A CL, one of the flexibilities under article 31 of the TRIPS agreement,[46] allows any country to authorize (by means of a decree, though this varies from country to country, for instance, the importation of generics under CLs also depends on national law) a national body to produce or import generic forms of a drug patented in the country. The third-party manufacturer must in return pay royalties to the patent holder.

In the case of HIV/AIDS, CLs have been effective in achieving price cuts. So far, they have mainly been used for HIV/AIDS drugs (first- and second-line regimens) but also for other therapies, such as cancer drugs. The countries that have so far issued CLs include Brazil, Canada, Ecuador, Eritrea, Ghana, India, Indonesia, Italy, Malaysia, Mozambique, Thailand, Zambia, and Zimbabwe.

"Based on data from Brazilian Ministry of Health, In 2007, Brazil issued a compulsory license for efavirenz, and the five-year savings were more than USD103 million," according to Marcela Cristina Fogaça Vieira. The results in Thailand were similar. They have been key to increasing countries' leverage in negotiating better prices with pharmaceutical companies, and to see more countries included by pharmaceutical companies in the geographical scope of their voluntary licenses.

The main objective of this VL is to bind generics producers, most of them in India, in order to prevent them from supplying any excluded MIC

However, although CLs have helped improve access, they have three central limitations. Firstly, they recognize a patent, and its legitimacy, despite the fact that the patent could in theory legally have been opposed if it was considered as not meeting patentability criteria on novelty. Secondly, they require the country that issues them to identify a generic supply solution as an alternative to branded products, and if the majority of manufacturers have signed a voluntary license with the patent holder for the same drug, or if the raw materials and active pharmaceutical ingredients (API) are also controlled by originator companies, then that complicates supply opportunities for countries that have issued the CL. This is a perfect illustration of the dangers and limitations of resorting to voluntary licenses, as they undermine a country's options to use the flexibilities provided under the TRIPS agreement.[47]

Finally, CLs, although permitted by the TRIPS agreement, render countries that use them vulnerable to pressure and threats from pharmaceutical companies or developed countries themselves. As shown in the WikiLeaks cables published in 2011,[48] Merck and the American diplomatic service had exerted pressure on Thailand to try and dissuade its government from issuing CLs for efavirenz, which was initially marketed by Merck. In 2007, after Thailand had issued a compulsory license on lopinavir/ritonavir, the originator company Abbott/AbbVie threatened to leave and stop the registration of its products in Thailand.

Furthermore, many MICs are currently negotiating free-trade agreements with the European Union or, through the Trans-Pacific Partnership (TPP), with the United States—agreements with which the European Union and the United States are trying to strengthen the intellectual property rights of these MICs, through provisions that could limit the use of TRIPS flexibilities, at the expense of people's right to health.

CONCLUSION

Clinical trial results suggest that new HCV treatments will significantly improve quality of life for people with HCV, and greatly increase their chances of achieving a complete and lasting cure. While representing major improvements over existing therapies, these drugs are not necessarily scientific innovations that fulfill patentability criteria, and so would not deserve patent exclusivity for 20 years. In order to ensure that generics competition is encouraged and to drive down the cost of these treatments, it is essential that patents on the new drugs are not granted in the case of not truly novel inventions. National patent offices should investigate applications for patents carefully in light of patentability criterias and novelty requirements, such as those under the Indian patent law. In countries, where the patentability criterias are not as clear as the Indian Section 3(d), patent law reforms should be encouraged to make sure that only real novelties are rewarded with a patent. International agencies should actively encourage countries to use the full range of flexibilities available under the TRIPS agreement and oppose strategies, such as voluntary licensing, that accept that the majority of people who need these drugs will not have access to them: even if voluntary licenses for these compounds were issued using the widest geographic scope ever granted for HIV/AIDS drugs, less than half of people with HCV worldwide would on the paper benefit. As for tiered pricing, this strategy is based purely on the commercial logic of turning a maximum profit, and goes far beyond securing a return on investment. Real production costs for new drugs confirm this: the prices demanded by companies are nothing short of indecent. Simply trying to cover expensive R&D and clinical trial costs do not justify them, particularly insofar as some of them are based on substances that are already known.

In an economic environment where there is no guaranteed access to healthcare, even in rich countries, let alone medical coverage in MICs, it would be criminal to leave the vast majority of people with HCV excluded from access to healthcare on the pretext that they live in less poor countries. Using generics should be encouraged in LICs and MICs as well as in HICs, since, as was shown with HIV/AIDS, only competition among several manufacturers can guarantee a significant reduction in the cost of treatment. In the richest countries, the price of health products should be challenged and subject to public debate and the current model of R&D questioned.

In the early 2000s, the WHO supported access programs, such as the Accelerating Access Initiative, on a very small scale. The Initiative covered a few thousand people living with HIV in the poorest countries, while millions of others continued to die. This “access” program consisted of negotiating prices between the branded pharmaceuticals industry and the poorest countries, for a limited number of people. In the Accelerating Access “progress report” of June 2002, we learned that only 27,000 people were able to access triple therapy through this program, under the pretext that it was only a pilot program.[49] Thirteen years later, over 10 million people have initiated antiretroviral therapy worldwide. This clearly proves that universal access to treatment is possible, despite the defeatist attitude of some at the end of the 1990s and beginning of the 2000s, even at UN agencies. Access to health is also a matter of strong political will, and a refusal to get caught up in the short-term vision and pseudo-pragmatic discourse that tolerates excluding millions of people from treatment and denying them the highest attainable standard of the right to health.

ENDNOTES

1. World Health Organization. Hepatitis C: fact sheet no. 164. 2013 July. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/. Epidemiological data vary greatly from one report to another. Daniel Lavanchy (see endnote 4) puts forward the figure of 158 million. Given the lack of HCV testing, these estimates will need to be adjusted based on future studies.

2. Treatment Action Group. Guide to hepatitis C for people living with HIV. New York: Treatment Action Group; 2009 October. Available from: http://www.treatmentactiongroup.org/sites/g/files/g450272/f/HCV-09updateENG.pdf. Forty-five percent of HIV-negative people who are infected with HCV clear the virus naturally within six months of being infected, compared with 20 percent for HIV-positive people; the remaining 55 percent have what is known as a chronic HCV infection.

3. MSF Access Campaign. Diagnosis and treatment of hepatitis C: a technical landscape. Geneva: Médecins Sans Frontières; 2013 April.

4. Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int. 2011 July Suppl 2; 31: p. 30-60.

5. Kershenobich D, Razavi HA, Sanchez-Avila JF, Bessone F, Coelho HS, Dagher L, et al. Trends and projections of hepatitis C virus epidemiology in Latin America. Liver Int. ; 31 Suppl 2: p. 18-29.

6. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, AlOmair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int. 2011; 31 Suppl 2: p. 61-80.

7. Available from: http://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

8. Available from: http://data.worldbank.org/about/country-classifications/world-bank-atlas-method.

9. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011 Feb;17(2):107–15. doi: 10.1111/j.1469-0691.2010.03432.x.

10. Available from: http://www.msfaccess.org/sites/default/files/AIDS_Report_UTW16_ENG_2013.pdf.

11. Available from: http://www.medicinespatentpool.org/wp-content/uploads/Gilead-MPPF+Non-Excl+License+Agmt+FINAL+-+with+amendments.pdf.

12. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries. Clin Infect Dis. 2014 Feb 13. Available from: http://cid.oxfordjournals.org/content/early/2014/01/06/cid.ciu012.full.pdf.

13. The social security financing Act (projet de loi de financement de la sécurité sociale) sets measures and objectives of the health insurance, pension insurance and provides public health goals for the country. It also estimates the total annual health budget of the State proposed by the government at the Parliament for adoption. For year 2014 see: http://www.securite-sociale.fr/LFSS-2014; The currency calculations were made based on the rate of the US dollar between November 2013 and January 2014.

14. Bouscaillou, J., et al. Hepatitis C among people who inject drugs in Tbilisi, Georgia: An urgent need for prevention and treatment. International Journal of Drug Policy (2014), http://dx.doi.org/10.1016/j.drugpo.2014.01.007

15. Kaplan K. Low- and middle-income countries defuse hepatitis C, the “viral time bomb.” In In: Treatment Action Group. 2013 Pipeline Report. New York: Treatment Action Group; 2013 June. Available from: http://www.pipelinereport.org/2013/hcv-global-access

16. See the press statement “Pharma refuses to ensure access to lifesaving hepatitis C treatment at global meeting” (28 February 2014) released by activists after the 1st HCV Community Advisory Board (CAB) that took place in Bangkok on February 22-25 2014 http://www.hepcoalition.org/spip.php?article79&lang=en

17. AbbVie has never opted out of VLs for HIV/AIDS drugs.

18. Drucker E, Alcabes PG, Marx PA. The injection century: massive unsterile injections and the emergence of human pathogens. Lancet. 2001 Dec 8;358(9297):1989–92. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(01)06967-7/fulltext. The reasons behind the very high HCV prevalence rate in Egypt are largely related to the consequences of vaccination campaigns conducted in the country with unsterilized equipment.

19. Lavanchy D. Evolving epidemiology of hepatitis C virus. All these figures are taken from this study, as are those related to prevalence rates by country.

20. The classification criteria used by the World Bank for these countries are available on its website: http://data.worldbank.org/about/country-classifications. The categories proposed are “High Income,” “Upper Middle Income,” “Lower Middle Income,” and “Low Income,” calculated based on the gross national income (GNI) per country per capita.

21. For instance, during the 1st HCV Community Advisory Board (CAB) that took place in Bangkok on February 22-25 2014, companies, such as Roche and Merck who have been marketing PEG-IFN for years, refused to disclose their prices in countries.

22. The life expectancy in Kenya is 60 and 71 in Cambodia.

23.See the eligibility criteria for the Global Fund to Fight AIDS, Tuberculosis and Malaria. Available from: http://www.theglobalfund.org/en/fundingmodel/updates/2014-02-04_Eligibility_List_for_2014_now_available.

24. Cf. “48 million Americans without health insurance” http://money.cnn.com/2013/09/17/news/economy/health-insurance-census/index.html?iid=EL

25. Cf. the infographic “15% of Americans living in poverty” http://money.cnn.com/2013/09/17/news/economy/poverty-income/

26: http://www.bloomberg.com/news/2014-03-10/sun-pharma-ranbaxy-recall-some-generic-drug-batches-in-u-s-.html

27. For relevant figures, see http://www.aphp.fr/aphp/les-chiffres-clefs.

28. Global Fund to Fight AIDS, Tuberculosis and Malaria. Spreadsheet of donor country pledges 2000–2010. Available from: http://www.theglobalfund.org/en/partners/governments.

29. This comparison also puts things into perspective regarding the real level of commitment of France to fight the 3 diseases in LMIC the past decade

30. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries. Clin Infect Dis. 2014 Feb 13. Available from: http://cid.oxfordjournals.org/content/early/2014/01/06/cid.ciu012.full.pdf.

31. Gilead Sciences Inc. Press release: Gilead Sciences to acquire Pharmasset, Inc. for $11 billion. 2011 November 11. Available from: http://www.gilead.com/news/press-releases/2011/11/gilead-sciences-to-acquire-pharmasset-inc-for-11-billion#sthash.E45FQzmK.dpuf.

32. Gilead's stock has doubled from USD42 in march 2013 to USD80 in march 2014. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-shareholderCenter

33. Bloomberg: *"Gilead CEO Becomes Billionaire on $84,000 Hepatitis Drug" (...) He owns 4.2 million shares of Gilead and 6.4 million vested options, according to filings with the U.S. Securities and Exchange Commission"*.Mar 4, 2014 http://www.bloomberg.com/news/2014-03-03/gilead-ceo-becomes-billionaire-on-84-000-hepatitis-drug.html

34. Moon S. Is the Global Fund heading backwards on access to medicines? PLOS speaking of medicine blog. 2013 December 1. Available from: http://blogs.plos.org/speakingofmedicine/2013/12/01/is-the-global-fund-heading-backwards-on-access-to-medicines.

35. Datta, P.T.J. Gilead, local generic players in talks.

36. MSF Access Campaign. Untangling the web of antiretroviral price reductions. 16th ed. 2013 July. Annex 3: spotlight on voluntary licenses. Available from: http://utw.msfaccess.org/.

37. AbbVie is currently developing at combo on HCV including 2 DAAs and ribavirin (ABT-450/R/267 + ABT-333 ± RBV). At equal prices, availability and cured results, other combinaison might be preferred

38. The sixteen countries added from one license to another are mainly islands for which there are also few or no data on HIV/AIDS.

39. Prasad R. India rejects patent claims on two HIV/AIDS drugs. The Hindu. 2009 September 7. Available from: http://www.thehindu.com/sci-tech/health/india-rejects-patent-claims-on-two-hivaids-drugs/article15145.ece.

40. Indian Patent Act, 1970, on "inventions not patentable" (chapter II): «What are not inventions.—The following are not inventions within the meaning of this Act,— [...] (d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.» Available from: http://ipindia.nic.in/ipr/patent/eVersion_ActRules/sections/ps3.html.

41. Waning B, Diedrichsen E, Moon S. A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. J Int AIDS Soc. 2010 Sep 14;13:35. Available from: http://apps.who.int/medicinedocs/en/m/abstract/Js19162en.

42. Source : « background paper «Data on prices, regulatory status, tariffs, and the intellectual property situation of key HIV treatments», prepared by the World Health Organization in collaboration with the Medicines Patent Pool for the Consultation on access to HIV Medicines in middle-income countries, 10 – 12 June, 2013, Brasília, Brazil »

43. From I-MAK's summary of the TDF opposition in India, available from http://www.i-mak.org/storage/TDF_Opposition_Summary.pdf: "Under s25(1) of the Indian Patents (Amendment) Act ("Act"), any person may legitimately file an opposition to the grant of a patent application based on a number of grounds available. These include, but are not limited to, proving that the claimed invention had already been published; that the invention claimed does not involve any inventive step and would have been obvious to a person working in the relevant field; or that the claimed invention simply does not meet the definition of an invention under the Act. With respect to the last ground, it is important to note that India has adopted a unique provision that states: "new forms of a known substance which do not result in the enhancement of the known efficacy of that substance" are not inventions and, therefore, are not patentable. For this purpose, 'salts' of a known substance shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy."

44. I-MAK. The roadmap: The HIV drug pipeline and its patents. August 2013. Available from: http://www.i-mak.org/roadmap.

45. http://www.thepharmaletter.com/article/i-mak-challenges-gilead-sofosbuvir-patent-in-india

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46. World Trade Organization. TRIPS Agreement, Part II, Section 5, Article 31. Available from: http://www.wto.org/english/docs_e/legal_e/27-trips_04c_e.htm.

47. I-MAK. Implications of the patent pool licenses with the Gilead. 2011 July 25. Available from: http://www.i-mak.org/i-mak-blog-updates/2011/7/25/implications-of-the-patent-pool-licenses-with-gilead.html.

48. WikiLeaks. Cables about Thailand. 2007 January 25. Available from: https://www.wikileaks.org/plusd/cables/07BANGKOK524_a.html.

49.Accelerating Access Initiative. Widening access to care and support for people living with HIV/AIDS: progress report. 2002 June. Available from: http://www.who.int/hiv/pub/prev_care/en/isbn9241210125.pdf.