



AT THE EDGE OF A MIRACLE

THE HEPATITIS C VIRUS (HCV)
EPIDEMIC IN MALAYSIA

HCV

A SITUATIONAL REPORT



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Author biographies

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Fifa Rahman is a Manager on a HCV – Access and Affordability project at the Malaysian AIDS Council. She is a health policy strategist, working on the intersection of health and law. She has a Master of Health Law from the University of Sydney, and has spoken at and attended numerous international fora on evidence-based drug policy and the impact of intellectual property in trade on access to medicines. These include the World Health Assembly, the International AIDS Conference, and the Global Congress on IP and the Public Interest. She is a reviewer for the International Journal of Prisoner Health, and is an alumni of the U.S. Department of State International Visitor Leadership Program (IVLP) with a focus on HIV, Pharmaceuticals, and Global Governance. In February 2017, she commenced a PhD studentship at the University of Leeds on international trade and access to medicines.

Marcela Fogaça Vieira is a human rights lawyer, specialized in intellectual property law, and holds a master's degree on public health on the topic of alternative models of R&D on health. She has been working on IP and access to medicines issues since 2005, as a member of the Working Group on Intellectual Property of the Brazilian Network for the integration of the Peoples (GTPI/Rebrip).

Professor Dr Rosmawati Mohamed is a Consultant Hepatologist at the University Malaya Medical Centre. Internationally and regionally, she had been appointed as Co-chairperson of the WHO Global Strategic and Technical Advisory Committee for Viral Hepatitis since 2014, Executive Council Member of the Coalition to Eradicate Viral Hepatitis in Asia Pacific since 2010, Council Member of International Coalition of Hepatology Education Providers since 2013, temporary Advisor to the WHO Western Pacific Region for Viral Hepatitis since 2014 and committee member of the Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver since 2008. Locally, she is the Deputy Master, Academy of Medicine of Malaysia.

Sergiy Kondratyuk is legal specialist on IP and access to medicines of the All-Ukrainian Network of PLWH (people living with HIV). Mr. Kondratyuk earned his law degree with honors in 2006 from the National Technical University Kyiv Polytechnic Institute Faculty of law, where he specialized in intellectual property and business law. In his current position he participates in development and advocacy for approval of Compulsory Licensing Regulation by the Ukrainian government; coordinates civil society anti-corruption monitoring of state procurement of antiretroviral (ARV) and anti-Tuberculosis (TB) medicines; helped draft the Law on Amendments to the Law of Ukraine on HIV/AIDS and related laws (the bill is registered with the parliament); and provides legal support of implementation of the 10th round Global Fund Program in Ukraine, including drafting and control of implementation of contracts within the project, developing amendments of internal operational procedures, and addressing potential regulatory problems. His professional experience also includes four years of legal work in the private sector at leading law firm. He studied in the Masters Program in International Human Rights Law and Intellectual Property (LL.M.) at Lund University in Sweden, where he focused on the right to health, and his publications include lead authorship of the analytic report “Implementation of TRIPS-flexibilities to improve access to medicines in Belarus, Georgia, Moldova and Ukraine” [Eastern Europe and Central Asia Union of PLWH (ECUO)-Aids Fonds; available at <http://bit.ly/1brGizi>].

Shangeetha Thirumayni is working on a HCV-Access and Affordability project at the Malaysian AIDS Council. This project addresses the growing need for multiple stakeholders to understand their roles in HCV medicines market access. She has a Master in Regional Integration from University of Malaya. Her main areas of interest include pharmaceutical pricing, reimbursement, and market access.

Executive Summary

The hepatitis C virus (HCV) has long since been a neglected disease, given long latency periods before any chronic illness manifests, and the low cure rate and numerous side effects of the pegylated interferon-ribavirin treatment (hereinafter PEG-INF). However, of late, given the development of revolutionary drugs called direct-acting antivirals (DAAs) that can cure the disease in as little as 8 weeks, international interest, and with it, international financial investment, has peaked.

When we began this project, we realised that there was little consolidated information on the HCV situation in Malaysia, whether epidemiological reports, patient voices, or the diagnostics and treatment environment. This report seeks to fill that gap and be a useful tool for clinicians, civil society, policymakers, politicians, and other stakeholders working towards access and affordability of HCV diagnostics and medication.

In Malaysia, a number of studies have placed HCV prevalence at 0.98¹-2.5% of the general adult population, and at 67.1% among people who inject drugs.² In a 2009 study conducted among 552 people who use drugs who were not in treatment,

65.4% were seropositive for HCV, and out of those, 43.2% were co-infected with HIV.³ This means that Malaysia has a high HCV burden.

Sofosbuvir, the base DAA for a number of highly effective regimens, is patented in Malaysia, which means it must be sold at the originator companies' proposed Malaysian price (USD \$12,000 for twelve weeks of treatment). Given that it is estimated that the drug can be produced at USD \$171-360 for twelve weeks of treatment,⁴ at volume, pricing is likely to be based on maximisation of profit margins rather than any rational stratification based on country developmental levels (as claimed by pharmaceutical companies). In Chapter 1 of this report, we elaborate further on the controversies surrounding DAA prices, and in Chapter 5, we recommend how international intellectual property law can allow the use of more affordable generics for Malaysia's national HCV response. In Chapter 4, we look at the WHO Strategy and targets for HCV elimination, and in Chapter 5 we analyse whether we will reach these targets. Chapter 11 describes the recommendations produced as a result of the report, in both Malay and English.

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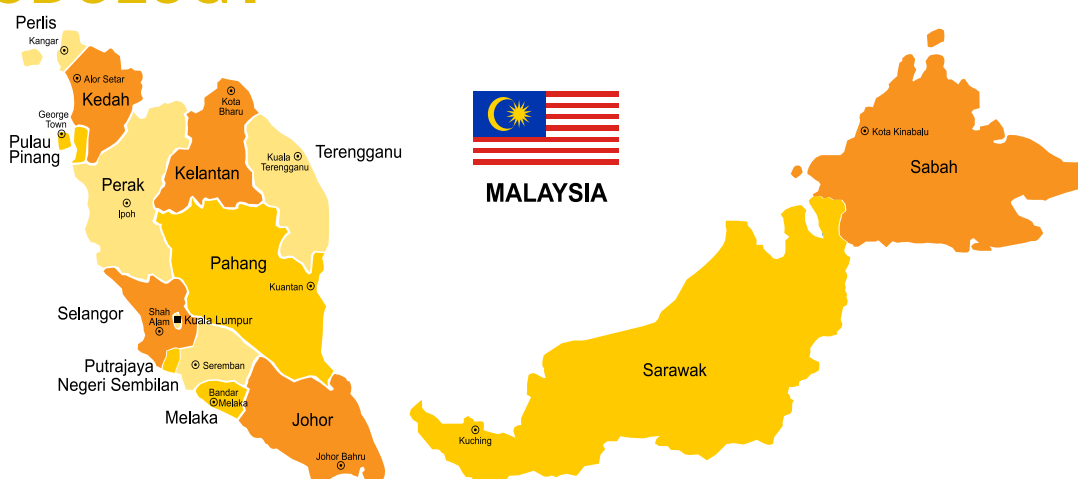
reviewed the drafts of this report and offered many suggestions to increase its accuracy, clarity and completeness: Henry Chang (Doctors of the World), Teri Roberts (Doctors without Borders/ Médecins Sans Frontières - MSF), Prof Dr Rosmawati Mohamed (University of Malaya Medical Centre), and Dr Tan Soek Siam (Selayang Hospital).

Glossary

| | |
|---|---|
| Decompensated cirrhosis | Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal hemorrhage, hepatic encephalopathy) or liver insufficiency (jaundice). ⁵ |
| In-vitro diagnostics (IVD) | A device, whether used alone or in combination, intended for the examination of specimens from the human body to detect diseases, conditions, or infections. These can be used in the laboratory, in clinical settings, and other tests are for consumers to use at home. |
| Sustained virological response (SVR) | SVR defined as aviremia 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection ⁶ , i.e. where the virus is not detected in the blood for a sustained period of time. |

1 Jamal R et al. unpublished data 2016
 2 Hser Y-I, Liang D, Lan Y-C, BK Vicknasingam, Chakrabarti A. Drug abuse, HIV, and HCV in Asian countries. *J Neuroimmune Pharmacol* 2016. DOI 10.1007/s11481-016-9665-x
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METHODOLOGY



The production of this report involved a review of secondary data from various sources, including the WHO, European clinical guidelines, academic medical journals, and newspaper articles pertaining to HCV and access to medicines. To compile patient perspectives, we identified patients with the assistance of hepatologists and gastroenterologists, and via semi-structured questionnaires, asked them about their diagnostics and treatment experiences. Clinicians were interviewed with a structured open-ended questionnaire.

| Indicator | Amount | Indicator | Percentage (%) |
|--|---|---|-------------------|
| GNI per capita (2015) | USD \$10,570.00 ⁷ | HCV Prevalence | 2.5 ⁸ |
| GDP per capita (PPP) (2015) | USD \$26,891.40 ⁹ | Public Health Expenditure as percentage of GDP (2014) | 2.3 ¹⁰ |
| Median monthly Household Income (2014) | USD \$1,049.48 (RM 4, 585) ¹¹ | HIV prevalence - age 15 to 49 | 0.4 ¹² |
| Purchasing power per capita | USD \$4,416.61 (RM 19, 733) ¹³ | | |

In 2016, the total population of Malaysia is estimated at 31.7 million persons.¹⁴ Malaysians spend 31.2 % of their disposable income on food.¹⁵ They also fork out 35% of their income to pay for their healthcare services and medical bills.¹⁶ The WHO (World Health Organisation) has advised Malaysia to reduce it because this could lead to financial catastrophe.¹⁷ Currently, Malaysia does not have a unified system of universal access to healthcare for its citizens.¹⁸ The healthcare system in Malaysia is a two-tiered system consisting of: (1) government-led and funded public sector, where it caters up to almost 65% of its population and (2) private sector.¹⁹ It is estimated that there are about ~140 public hospitals²⁰ and ~209 private hospitals in Malaysia.²¹

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Chapter 1

The HCV landscape in focus: making the case for investment in DAAs

Fifa Rahman

Across the world, the introduction of all-oral therapies for HCV have resulted in renewed interest and programming towards the elimination of HCV. This interest, however, has been accompanied by international outrage at the prices of these drugs. So while they achieve higher cure rates over a much shorter course of time, and have low side effects, the prices of these drugs place them far and beyond the access of the ordinary patient. In Malaysia, while there is presently no national viral hepatitis plan, commitment by health officials is encouraging, and there is an on-going clinical trial testing pan-genotypic DAA regimens that has increased focus in this area. However, restricted fiscal space means that the government may not necessarily be able to invest in branded DAAs. This chapter briefly describes HCV epidemiology in Malaysia, dissects price controversies on DAAs, and makes the case for investment in DAAs.

Di seluruh dunia, sejak terapi oral keseluruhan untuk rawatan HCV (DAA) diperkenalkan, telah timbul minat dan juga program ke arah usaha menghapuskan HCV. Minat ini, walau bagaimanapun, telah diiringi kemarahan di peringkat antarabangsa atas harga DAA yang tinggi. Sungguhpun DAA dapat mencapai kadar penyembuhan yang lebih tinggi dalam tempoh rawatan yang lebih singkat, dan mempunyai kurang kesan sampingan, faktor kos yang tinggi menyebabkan ubat-ubatan ini berada di luar kemampuan pesakit biasa. Di Malaysia, walaupun pada masa ini masih belum ada pelan viral hepatitis kebangsaan, komitmen daripada pegawai-pegawai atasan di Kementerian Kesihatan adalah menggalakkan. Percubaan klinikal untuk rejimen DAA pan-genotip juga berterusan yang telah meningkatkan fokus terhadap bidang ini. Walau bagaimanapun, ruang fiskal yang terhad bermakna kerajaan mungkin tidak mempunyai sumber yang cukup untuk membiayai kos DAA yang berjenama. Bab ini menerangkan secara ringkas epidemiologi HCV di Malaysia, merungkai kontroversi harga DAA dan menghuraikan mengapa perlu pelaburan kesihatan dibuat terhadap ubat-ubatan DAA.

The epidemiological landscape of HCV in Malaysia

Scholarly literature in Malaysia is overwhelmingly focused on prevalence. For example, in 1993, the year that Malaysia started screening blood donations for HCV, in a study among 3540 blood donors, 1.49% tested HCV positive.²² A couple of more recent studies have attempted to estimate HCV prevalence in the general population. Unpublished data from a sample of 1016 patients from The Malaysian Cohort, a cohort of 106,527 participants, showed that 10 patients were seropositive for HCV (0.98%).²³ Meanwhile, another study estimates that there are 454,000 HCV seropositive patients in Malaysia, representing 2.5% of the general population.²⁴ A chronological illustration of data from prevalence studies is shown below:

| Year | 1993 | 2014 | 2016 |
|----------------|---------------------------------|---|---|
| Prevalence (%) | 1.49 | 2.50 | 0.98 |
| Sample | 3540 blood donors ²⁵ | Estimation using Multi-parameter evidence synthesis (MEPS) of multiple data sources ²⁶ | 1,106 individuals, cluster sampled from 106,527 Malaysian Cohort participants ²⁷ |

Table 1.1: Chronological Illustration of Data from HCV Prevalence Studies

Several studies have been done to determine seroprevalence in specific populations. For example, in 1998, in a population of 85 transfusion dependent thalassaemics, 22.4% tested positive for HCV;²⁸ in a 4-year study among 1157 patients with clinical and biochemical evidence of liver disease in Northeast Malaysia, 5.4% were HCV antibody positive;²⁹ and in a small urban sample, 0.6% of children tested HCV positive.³⁰

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23 Jamal R et al. unpublished data 2014

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25 Duraisamy G et al. Prevalence of hepatitis C antibodies in blood donors in Malaysia. Med J Malaysia 1993; 48(3): 314-316.

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Among people who inject drugs (PWID), Malaysian prevalence estimates are at least 50%,³¹ with one study estimating HCV prevalence among PWIDs at 67.1%.³² In a 2007 speech by the then-Minister of Health Datuk Seri Chua Soi Lek, he stated that 89.9% of persons dependent on heroin enrolled in treatment were HCV positive.³³ In a 2009 study conducted among 552 people who use drugs who were not in treatment, 65.4% were seropositive for HCV, and out of those, 43.2% were co-infected with HIV.³⁴ In a 2014 study estimating general prevalence, it was found that among males of Malay ethnicity, for 77%, the route of probably transmission was active or a previous history of injecting drug use.³⁵

HIV/HCV Co-Infection

Given that HIV and HCV have overlapping modes of transmission, co-infection is a significant public health concern. A recent study estimates that there are 2.3 million people worldwide who are co-infected with HIV and HCV.³⁶ In a 2009 study conducted among 552 Malaysian people who use drugs who were not in treatment, 65.4% were seropositive for HCV, and out of those, 43.2% were co-infected with HIV.³⁷

In the TreatASIA study, among a cohort of 7,455 HIV patients recruited from HIV treatment centres in 12 countries (including Malaysia), found that patients with HCV co-infection had lower CD4 counts and poorer survival than HIV mono-infected patients,³⁸ and emphasised the importance of scaling up screening, including confirmatory HCV screening. In a small retrospective observational cohort study conducted in Sungai Buloh Hospital in Malaysia, the authors noted the efficacy of a treatment regimen of pegylated interferon-ribavirin in HIV/HCV co-infected patients, but noted key treatment difficulties where the patient was also co-infected with tuberculosis or where the patient was cirrhotic.³⁹ In considering experiences

of adverse effects, the authors flagged direct-acting antivirals (DAAs) as having better side-effect profiles, but a significant cost challenge.⁴⁰

In developed nations, given the adoption of interferon-free all-oral DAA regimens which have high SVR rates even in cirrhotic co-infected patient populations, it has been recommended that 'HIV/HCV co-infected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications'.⁴¹ This statement highlights a simplified approach to treatment with the highly effective DAAs. In addition, given that some DAA treatments are pan-genotypic, the necessity for a genotype test dissipates.

Direct-Acting Antivirals (DAAs) and Price Controversies

Sofosbuvir (brand name Sovaldi™ by Gilead Sciences), described as a 'game-changing drug',⁴² is the base drug for highly effective and safe HCV drug combinations, was approved by the US Food and Drug Administration (FDA) at the price of USD \$84,000 (MYR 351,027.60) for a 12-week cure regimen.⁴³ Developed by Pharmasset, with initial research starting in 2008, the company (and relevant molecules with it) were purchased by Gilead on 17 January 2012.⁴⁴

This announcement resulted in widespread backlash from governments, patients, and international health organisations. It has been labelled as 'the poster child of a U.S. health care system that is being bankrupted by greed'⁴⁵ and a 'revolution' that comes with a 'big fat asterisk... in the form of a bomb that destroys health-care budgets.'⁴⁶ Outrage continued with the discovery that DAAs (including sofosbuvir) could be produced at USD \$100-250 per 12-week treatment cost.⁴⁷

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- 43 U.S. Food and Drug Administration approves Gilead's Sovaldi (sofosbuvir) for the treatment of chronic hepatitis C. Gilead [Press Release – Internet]. 2013 Dec 6 [cited 2016 Oct 25]. Available from: <http://www.gilead.com/news/pressreleases/2013/12/us-food-and-drug-administration-approves-gileads-sovaldi-sofosbuvir-for-the-treatment-of-chronichepatitis-c>
- 44 Wyden R, Grassley CE. The price of Sovaldi and its impact on the U.S. health care system. U.S. Senate Committee on Finance [Internet]. 2015 Dec [cited 2016 Oct 25] at 123. Available from: [http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20\(Full%20Report\).pdf](http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf)
- 45 Sachs J. The pharma drug that is bankrupting America. *Alternet/Huffington Post* [newspapers on the Internet]. 2015 Feb 17 [cited 2016 Oct 25]. Available from: <http://www.alternet.org/drugs/pharma-drug-bankrupting-america>
- 46 Picard A. The cure for hepatitis C is upon us, but at a costly penny. *The Globe and Mail* [newspaper on the Internet]. 2014 Apr 27 [cited 2016 Oct 25]. Available from: <http://www.theglobeandmail.com/life/health-and-fitness/health/the-cure-for-hepatitis-c-is-upon-us-but-at-a-costly-penny/article18224668/>
- 47 Hill A, Khoo S, Fortunak J et al. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clinical Infectious Diseases* (2014) doi: 10.1093/cid/ciu012

On 1 December 2015, after an 18-month investigation by the U.S. Senate Committee on Finance, U.S. Senators Grassley and Wyden released a report⁴⁸ into Gilead Sciences and Sovaldi™, finding that prices were determined based on revenue⁴⁹ and that Gilead did not consider research or production costs as major factors in setting the price.⁵⁰

This means that if we compare the cost of developing sofosbuvir with Gilead’s revenue in both 2014 and 2015, assuming that the same amount of products are sold per day, it would take 4.35 days to recoup the cost. And if we were to compare the total cost of developing sofosbuvir combined with the cost to purchase Pharmasset, then compare that with revenue, it would

In fact, the Gilead executive who led the price recommendations stated that he did not know the cost of manufacturing the drug.⁵¹

In its first quarter of sales of Sovaldi™, Gilead Sciences broke the record for highest sales of a drug with USD \$2.3 billion takings.⁵² The following illustrations are useful to further contextualise Gilead’s earnings from sofosbuvir-based regimens (both Sovaldi and Harvoni), as compared to research and development cost:

take 263.49 days to recoup the cost. From these calculations, it can be seen that Gilead has recouped the cost of R&D and acquisitions, and the only justification for continuing their arbitrary pricing is profit.

| | | |
|---|---|------------------------------------|
| 1 | Cost of developing sofosbuvir (Pharmasset data) | USD \$188 million ⁵³ |
| 2 | Cost of Gilead’s purchase of Pharmasset | USD \$11.2 billion |
| 3 | U.S. Federal support to develop sofosbuvir (tax \$) | USD \$4.2 million ⁵⁴ |
| 4 | Gilead Sciences sofosbuvir-based revenue 2014 | USD \$12.41 billion |
| 5 | Gilead Sciences sofosbuvir-based revenue 2015 | USD \$19.14 billion ⁵⁵ |
| 6 | Gilead Sciences sofosbuvir-based revenue first half of 2016 | USD \$ 8.216 billion ⁵⁶ |

Table 1.2 : Gilead’s Earnings from Sofosbuvir-based Regimens as compared to research and development cost

4.35 DAYS
 The amount of time needed to recoup cost of developing sofosbuvir

EXPLANATORY NOTE

‘... Pharmasset reported \$62.4m specifically for developing sofosbuvir from preclinical research to phase II trials. At this stage, Pharmasset identified a future budget of \$125.6m for taking sofosbuvir through phase III trials and FDA approval, bringing the compound’s total past and projected development costs up to \$188m.’

*~Roy and King, 2016
 British Medical Journal*

48 Wyden R, Grassley CE. op. cit.
 49 Wyden R, Grassley CE. op. cit., p. 44.
 50 Wyden R, Grassley CE. op. cit., p. 21, 44.; Bejoy R. Anger at huge price tag for life-saving medicine. GroundUp [Internet]. 2016 Jul 28 [cited 2016 Oct 25]. Available from: <http://www.groundup.org.za/article/anger-huge-price-tag-life-saving-medicine/>
 51 Wyden R, Grassley CE. The price of Sovaldi and its impact on the U.S. health care system. U.S. Senate Committee on Finance [Internet]. 2015 Dec [cited 2016 Oct 25] at 117. Available from: [http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20\(Full%20Report\).pdf](http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf)
 52 Pollack A. Gilead revenue soars on hepatitis C drug. The New York Times [newspaper on the Internet]. 2014 Apr 22 [cited 2016 Oct 25]. Available from: <http://www.nytimes.com/2014/04/23/your-money/gilead-revenue-soars-on-hepatitis-c-drug.html>
 53 Roy V, King L. Betting on hepatitis C: how financial speculation in drug development influences access to medicines. BMJ 2016;354:i3718 doi: 10.1136/bmj.i3718
 54 Gilead Sciences: price gouger, tax dodger. Americans for Tax Fairness [Internet]. 2016 Jul [cited 2016 Oct 25]. Available from: <http://www.americansfortaxfairness.org/files/ATF-Gilead-Report-Finalv3-for-Web.pdf>
 55 Gilead Sciences Announces Fourth Quarter and Full Year 2015 Financial Results. Gilead [Press Release – Internet]. 2016 Feb 2 [cited 2016 Oct 25]. Available from: <http://www.gilead.com/news/press-releases/2016/2/gilead-sciences-announces-fourth-quarter-and-full-year-2015-financial-results>
 56 Gilead Sciences Announces Second Quarter 2016 Financial Results. Gilead [Press Release – Internet]. 2016 Jul 25 [cited 2016 Oct 25]. Available from: <http://www.gilead.com/news/press-releases/2016/7/gilead-sciences-announces-second-quarter-2016-financial-results>

It has been claimed that Gilead bases its pricing of sofosbuvir based on income levels of countries, specifically, correlating it with GNI per capita. For example, how Brazil at USD \$9,850 GNI per capita gets sofosbuvir for USD \$7500, whereas Malaysia at \$10,600 GNI per capita gets sofosbuvir at USD \$12,000. However, a 2015 mapping of prices in 38 countries shows that there is little correlation between these two variables.⁵⁷ The graph from that study is reproduced below:

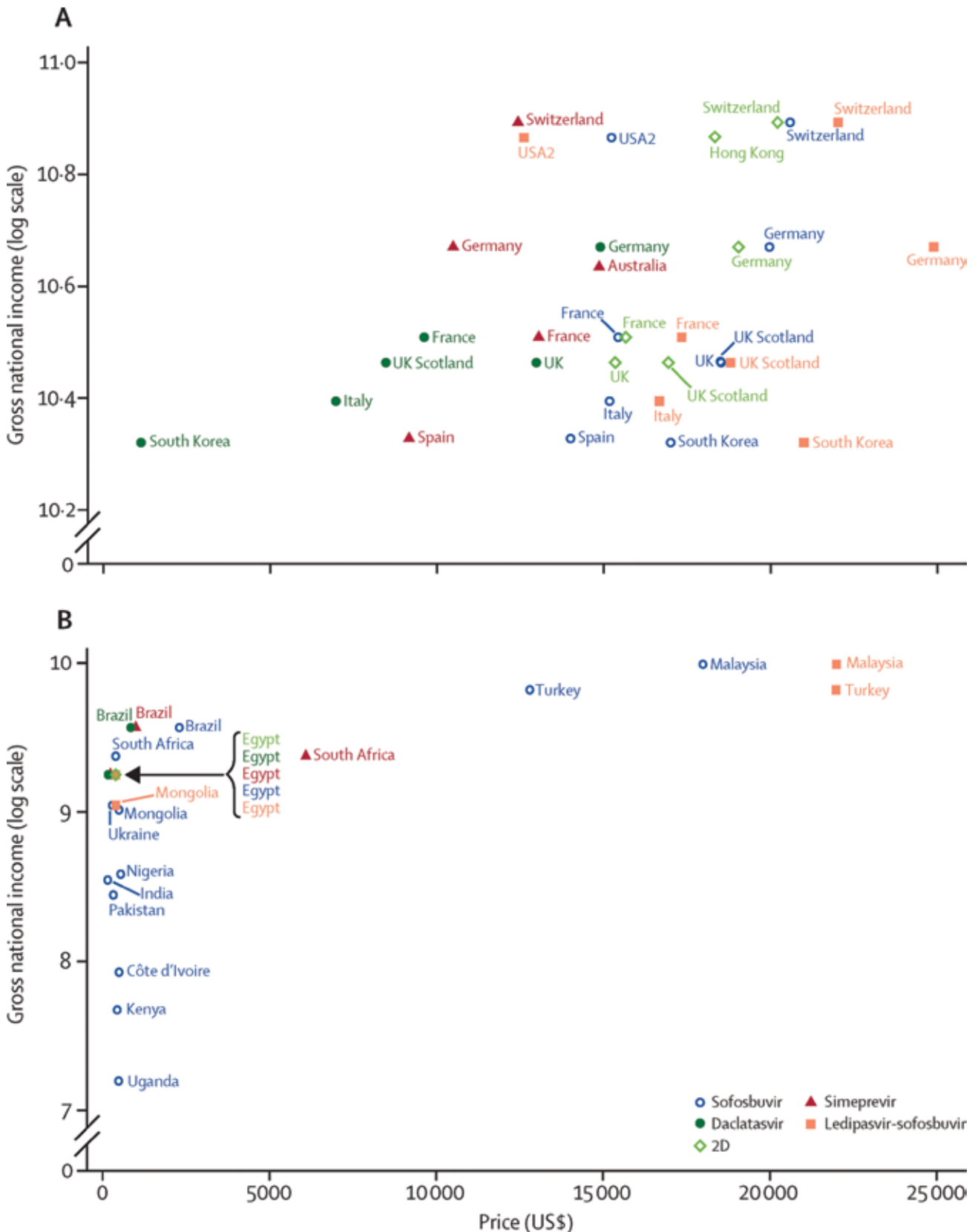


Figure 1.1: Correlation between drug prices and gross national income, cited from Andrieux-Meyer et al. 2015

57 Andrieux-Meyer I, Cohn J, Afonso de Araújo ES, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. The Lancet 2015; 3: e676-e677 at e676

Making the case for generic DAAs

The WHO Global Strategy on viral hepatitis (described in Chapter 2 of this Report) contains ambitious targets for Member States to achieve by 2020 and 2030. Among the targets proposed are that 30% of the estimated population living with HCV is diagnosed and that 50% of those eligible for treatment begin treatment for HCV⁵⁸ by 2020.

Using a modelling approach, Rosmawati M and Razavi H et al (personal communication) projected the future disease burden and developed treatment scenarios to control the disease burden related to Hepatitis C (HCV) in Malaysia. With the current preventive measures and HCV detection rate and treatment scenario of 550 persons treated each year, the number of prevalent HCV infections is projected to decrease slightly but the HCV-related disease burden would increase over time in parallel with the health costs of treating advanced liver disease and its complications.⁵⁹ The study showed that a substantial reduction, and even elimination of Hepatitis C as a major public health problem, is possible, with a combination of scaling up of HCV treatment with DAA agents with high cure rates, increased diagnosis and a reduction in HCV incidence.⁶⁰

With current government budgeting allocated to HCV, only 640 persons per year can be treated based on Gilead's proposed price for Malaysia (USD \$12,000). Based on the above estimation that there are 454,000 HCV seropositive persons in Malaysia, and data that only 550 persons treated per year, there is little doubt that the targets will not be reached.

There are several opportunities available to the Malaysian government in urgently scaling up treatment, the first of which is the use of government use licences (also known as a compulsory licence), which is a type of TRIPS flexibility. These licences, defined under international trade law, allow Member States to import generic medicines on grounds that they self-determine.⁶¹ They are described further in Chapter 5 of this report. Also in Chapter 5, we address the pervasive and irrational fear that issuing a compulsory licence will ignite the wrath of international trade hotshots, namely the United States and the European Union, and address other related myths.

Another opportunity is the DNDi clinical trial on pan-genotypicity of sofosbuvir-velpatasvir, which enables about 600 Malaysian patients to be treated and cured, while drawing attention to the affordability of the generic DAAs used in this trial. This trial is described in Chapter 4 of this report.

The generic medicines used in the trial are used under the research exemption also provided for under TRIPS. Once the trial draws to a close, however, Malaysia will still have to purchase branded sofosbuvir, unless a compulsory licence is issued, or Gilead reduces their price even further. A number of news articles have inaccurately described that this regimen will be affordable upon the conclusion of the trial.⁶²

Other naysayers question the cost-effectiveness of HCV treatment with DAAs. Rosmawati's study referred to above states that there will be cost-savings in terms of treatment for advanced liver disease, and years lost due to disability. A U.S.-based study found similar findings, and went further by stating that for genotype 3, sofosbuvir-ledipasvir-ribavirin would be cost-saving if sofosbuvir cost less than \$1500 per week.⁶³

Conclusion

At the baseline scenario, Malaysia will not achieve WHO targets by 2020, and will have to plan fiscally to deal with advanced liver disease and cirrhosis in the future. In addition, there will be an increased loss of years lost due to disability. Brand-name sofosbuvir has been priced with little correlation to research and development costs, or GNI per capita, as widely claimed, but rather with the sole objective of profit maximisation. In addition, as addressed elsewhere in this report, there are legal mechanisms to ensure Malaysians are able to access DAAs at affordable rates. Malaysia must act urgently to circumvent increasing burden of disease.

58 WHO-Western Pacific Region (WPRO). Regional action plan for viral hepatitis in the Western Pacific 2016-2020. [Internet] 2016 [cited 2016 Oct 25] at 7. Available from: http://iris.wpro.who.int/bitstream/handle/10665.1/13141/97892906177617_eng.pdf

59 Mohamed R, Razavi H. (upcoming) 2017.

60 Mohamed R, Razavi H. (upcoming) 2017.

61 TRIPS and health: frequently asked questions: compulsory licensing of pharmaceuticals and TRIPS. World Trade Organisation [Internet]. 2006 Sep [cited 2016 Oct 25]. Available from: https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm

62 Loh FF. Hepatitis C treatment at a fraction of the cost to be available soon. The Star Online [newspaper on the Internet]. 2016 Apr 14 [cited 2016 Oct 17].

Available from: <http://www.thestar.com.my/news/nation/2016/04/14/hepatitis-c-treatment-at-a-fraction-of-the-cost/>

63 Najafzadeh M, Andersson K, Shrank WH et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Annals of Internal Medicine* 2015 Mar 17; 162(6): 407-419.

Chapter 2

Making sense of the WHO international viral hepatitis targets – strategising for concerted action

Shangeetha Thirumayni and Fifa Rahman

The WHO has set ambitious targets for countries to achieve in the fight against viral hepatitis. Given current coverage of HCV services, many questions arise as to whether these targets are achievable. This chapter describes key sections of the WHO global strategy and how those might be integrated and strategised for in a Malaysian context.

Pertubuhan Kesihatan Sedunia (WHO) telah menetapkan beberapa sasaran yang tinggi terhadap negara-negara anggota dalam memerangi viral hepatitis. Sungguhpun begitu, memandangkan liputan semasa perkhidmatan HCV yang terhad, timbul banyak persoalan sekiranya sasaran-sasaran ini dapat dicapai. Bab ini menjelaskan seksyen-seksyen utama dalam strategi global WHO serta langkah-langkah penyepaduan dan penstrategian dalam konteks Malaysia.

About 1.46 million people have died due to viral hepatitis in 2013,⁶⁴ with 48 per cent of those deaths resulting from HCV.⁶⁵ According to the 2013 Global Burden of Disease Study, viral hepatitis has become the 7th leading cause of death in the world, killing more people in a year than HIV/AIDS, tuberculosis, or malaria,⁶⁶ with more than 58 per cent of viral hepatitis deaths occurring in upper middle-income and high-income countries.⁶⁷ There are a number of high-burden countries, including China, Pakistan, and Egypt, but worldwide, country-specific prevalence ranges from <1% to >10%.⁶⁸

Internationally, ambitious targets to eliminate HCV as a major public health threat have been launched. These targets come at an opportune time, where revolutionary DAAs are curing at faster and higher rates, and they set the scene for elimination of HCV as a major public health threat.

Applicable to Malaysia is the WHO Global Health Sector Strategy on Viral Hepatitis, 2016-2021⁶⁹ launched in the 69th World Health Assembly (hereinafter WHO Global Strategy) and the Regional Action Plan for Viral Hepatitis in the Western Pacific 2016–2020 (hereinafter the WPRO Regional Plan). Below is a summary of the 2020 targets:

| WHO Global Targets ⁷⁰ | WPRO Regional Targets ⁷¹ |
|------------------------------------|--|
| 30% reduction in new cases | 30% of estimated population diagnosed |
| 10% reduction in deaths | 50% of estimated population begun treatment |
| 3 million chronic patients treated | 90% of those on treatment, virally suppressed or cured |

Table 2.1: WHO 2020 International and Regional Targets.

These developments, however, did not occur in a vacuum. The fast-growing burden of disease led a small group of advocates in 2010 to achieve a major win in viral hepatitis – a designated day to draw global attention to the disease.⁷² Today, we call that day World Hepatitis Day, celebrated annually on 28 July.

In 2012, a WHO framework document⁷³ on the prevention and control of viral hepatitis infection was launched, and provided the first glimpse into a consolidated global vision of viral hepatitis. The launch of this document precipitated a gathering of civil society, professionals, and coalitions in North Asia to strategise implementation of the framework.⁷⁴

64 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ;at p.6. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016_04_eng.pdf

65 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. 2016 June . [cited 2016 Oct 18]; at p.11. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

66 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet.[Internet]. 2015 August 22. [cited 2016 November 18] 386: 743–800. Available from: [http://thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(15\)60692-4.pdf](http://thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)60692-4.pdf)

67 Wiktor S. The Global Burden of Viral Hepatitis: better estimates to guide hepatitis elimination efforts. World Health Organisation Media Center [Internet]. 2016 July 26. [cited 2016 November 22]. Available from: <http://www.who.int/mediacentre/commentaries/better-estimates-hepatitis/en/>

68 Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clinical Infectious Diseases. [Internet]. 2012 Jul 15;. [cited 2016 Oct 18] 55 (suppl 1):S10-5. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22715208>

69 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. 2016 June [cited 2016 Oct 18]; Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

70 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ;at p.6. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016_04_eng.pdf

71 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region [Internet]. 2015 Oct [cited 2016 Oct 18] at p.17. Available from: <http://www.wpro.who.int/hepatitis/resource/features/ravph/en/>

72 Farrell T. A make-or-break moment for the first viral hepatitis strategy. World Hepatitis Alliance [Internet]. 2016 May 26 [cited 2016 Oct 28]. Available from: <http://www.worldhepatitisalliance.org/news/may-2016/make-or-break-moment-firstviral-hepatitis-strategy>

73 World Health Organization. Prevention and Control of Viral Hepatitis Infection: Framework for Global Action [Internet]. 2012. [cited 2016 Oct 16]. Available from <http://www.who.int/hiv/pub/hepatitis/Framework/en/>

74 Chen D-S, Locarnini S, Wait S, Bae S-H, Chen P-J. Report from a Viral Hepatitis Policy Forum on implementing the WHO framework for global action on viral hepatitis in North Asia. Journal of Hepatology 2013; 59(5): 1073-1080

Four years later, at the 67th World Health Assembly, the 2014 resolution on viral hepatitis (WHA67.6)⁷⁵ was adopted, and called for an intensified and broader global response and for WHO Secretariat to examine the feasibility of eliminating HCV across the countries.

The WHO Global Strategy sets out a vision of elimination of viral hepatitis transmission and a world where ‘everyone has access to safe, affordable and effective prevention, care and treatment.’⁷⁶ Achieving these targets will require radical changes in domestic and global public health responses. The WHO Global Strategy cites universal health coverage, the continuum of services, and a public health response as the key frameworks for action.⁷⁷

In addition to targets, the Global Strategy as an overarching framework defines a set of priority actions and strategic directions for WHO and Member States to adhere to when formulating and assessing efforts aimed at eliminating HCV. Priority actions are categorised into five strategic directions, which are:⁷⁸

All strategic directions require joint efforts from the WHO and Member States.⁷⁹ Under Strategic Direction 2, the WHO states that countries must ‘define a set of essential viral hepatitis interventions... to be included in the national health benefit package.’⁸⁰ This would mean that the upcoming viral hepatitis national plan must include hepatitis services that are publicly funded.

The WHO Global Strategy also calls for Member States to implement their HCV response with the guidance of a structured national plan with clear accountability.⁸¹ At time of writing, Malaysia is still in the midst of drafting the national viral hepatitis plan. It is unclear whether civil society and patient groups have been involved in this process. Given the discovery of DAAs and the launch of the WHO Global Strategy, it is imperative also that the structure of the national plan accounts for these treatments and the simplified diagnostics that precede them.⁸²

In regard to diagnostics, Malaysian HCV patients often need to fork out their own money for comprehensive diagnostics.⁸³ While Malaysia has a heavily subsidised public health system, however, in 2010 26.8% of the population primarily accessed private services,⁸⁴ and even for those that do access the public health system, out-of-pocket payments are at 35.3%.⁸⁵ The WHO Global Strategy recommends the integration of viral hepatitis testing into national plans,⁸⁶ and emphasises that services must be made available to patients without them experiencing financial hardship.⁸⁷

In addition, the WHO Global Strategy also states that in designing high impact interventions, the selection of essential interventions and services should be through a transparent process.⁸⁸ It is suggested that this occur via a consultation, whereby all broad stakeholders such as government, service providers, patients, and civil society are engaged and kept in the loop.

Strategic direction 3 which focuses on equitable access calls for the integration and linkage of HCV services with other health services to accelerate the progress towards achieving WHO’s targets and increase efficiency, reach, acceptability and savings.⁸⁹ The 728 needle and syringe exchange programme (NSEP) outreach points throughout Malaysia⁹⁰ is an example of where this linkage could occur, for example in the form of the inclusion of HCV rapid testing at NSEP outreach points. This

| Strategic Direction | Explanation |
|---------------------|--|
| 1 | Information for focused action: developing a strong strategic information system to understand viral hepatitis epidemics and focus the response |
| 2 | Interventions for impact: defining essential, high-impact interventions on the continuum of hepatitis services that should be included in health benefit packages |
| 3 | Delivering for equity: strengthening health and community systems to deliver high-quality services to achieve equitable coverage and maximum impact |
| 4 | Financing for sustainability: proposing strategies to reduce costs, improve efficiencies and minimize the risk of financial hardship for those requiring the services |
| 5 | Innovation for acceleration: promoting and embracing innovation to drive rapid progress |

Table 2.2: WHO’s Strategic Directions for Viral Hepatitis 2016-2021

75 World Health Organization :Hepatitis C. In: 67th World Health Assembly [Internet]; 2014 May 24, [cited 2016 Oct 18]. Available from: http://www.wpro.who.int/hepatitis/wha67_r6-en.pdf.

76 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet] [Internet]. [cited 2016 Oct 18]; at p.9. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

77 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. 2016 May [cited 2016 Oct 18]; at p.9. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

78 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. [cited 2016 Oct 18]; at p. 8.. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

79 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. [cited 2016 Oct 18]; at p.7. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

80 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis.[Internet]. [cited 2016 Oct 18]; at p.29. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

81 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021 towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 28. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>.

82 From year 2012 to 2014, Malaysia has provided free pegylated interferon alfa 2a/2b with ribavirin (PEG-IFN/RBV) for approximately 500 HCV patients per year. Mohamed R, Razavi H et al. (upcoming) 2017.

83 Tan SS, Leong CL, Lee CK. Treating hepatitis C in HIV/HCV co-infected patients in Malaysia-the outcomes and challenges. The Medical Journal of Malaysia. [Internet]. 2015 Oct; [cited 2016 Oct 18]; 70(5): 281-7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26556116>

84 Chua HT, Cheah JC. Financing universal coverage in Malaysia: a case study. BMC Public Health. 2012 Jun 22; 12(1): 1

85 Boo SL. Malaysia warned high out –of-pocket expenses can cause catastrophe. Malay Mail [Internet]. 2016 June 2 [cited 2016 Oct 18]. Available from: <http://www.themalaymailonline.com/malaysia/article/malaysia-warned-high-out-of-pockethealth-expenses-can-cause-catastrophe>

86 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 36. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

87 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 14. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

88 Ibid at p. 29. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

89 Ibid at p. 38. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>.

90 Boo SL. Malaysia is ‘world leader’ in battling HIV spread with needles, says UK Report. Malay Mail [Internet]. 2015 Feb 17 [cited 2016 Oct 27]. Available from: <http://www.themalaymailonline.com/malaysia/article/malaysia-is-world-leader-inbattling-hiv-spread-with-needles-says-uk-report>

could potentially increase linkage to comprehensive screening and onward care for people who inject drugs. This suggestion is consistent with EASL Recommendations available in Chapter 3 of this report. Interviews with diagnostics companies indicate that there is a strong interest on their end to place rapid tests in these centres, as well as methadone clinics.

In further elaboration of this strategic direction, the WHO states that HCV services should be sufficient in order to cater to everyone who needs the service.⁹¹ This is easier said than done, however, with bureaucratic and financial restrictions impacting even the most forward-thinking HCV programs. France, for example, seen as a model country in HCV medicines access given their plan for universal access to DAAs,⁹² but is not excluded from delays and hiccups. In France, patients' access to DAAs is decided after multidisciplinary committee meetings.⁹³ This eventually causes delays in treatment of the diagnosed patients. French authorities stated that the slow growth in the number of people accessing HCV treatment is attributed to limited capacity of specialised consultation sessions.⁹⁴ From this, it can be seen that there is a strategic need to look for pragmatic solutions such as task shifting from specialists to primary care doctors and decentralisation of HCV care to overcome the limited capacity of hepatologists as HCV diagnostics and treatment regimes can be administered and monitored with less organisational support.⁹⁵ In considering experiences of best practice nations, it is crucial that limitations be considered in the context of Malaysian conditions, particularly, decreasing fiscal space.

Strategic Direction 5 in the WHO Global Strategy focuses on innovation throughout the continuum of prevention, diagnosis, and treatment to accelerate the HCV response,⁹⁶ and states that the innovations need to be supported with collaborative operational research. Crucially, it draws attention to the 'more effective, potent, tolerable and safer oral drugs' and that 'priority should be given to the development of affordable, simple pan-genotypic regimens for hepatitis C virus.'⁹⁷

The Drugs for Neglected Diseases initiative (DNDi) feasibility study⁹⁸ (described in Chapter 4 of this report) conducted in collaboration with the Malaysian government on testing the pan-genotypicity of sofosbuvir-velpatasvir is an example of innovative

collaborative research that aspires to translate into pan-genotypic treatment. DNDi, an innovative international public-private partnership develops drugs with funding from multiple sources. Together with Pharco Pharmaceuticals, they signed agreements covering the feasibility study and scale-up of HCV treatment regimen at a price of \$294 per course⁹⁹ and if the clinical trials are successful, there is a possibility for Malaysia to adopt this regime in its public health approach to treating HCV patients.¹⁰⁰ Making the trial much more affordable than marketed regimens is another example of innovation in practice. It should be noted, however, that more innovative practices will be needed to overcome patent barriers at the conclusion of the trial.

Besides that, Global Strategy also states there are huge opportunities to enhance the HCV's diagnostics technologies, strategies for expanding HCV testing services and ensuring accurate and reliable diagnosis.¹⁰¹ With the introduction of DAAs, there are real opportunities for simplifying the diagnostics environment, and ensuring that testing services can reach remote areas and difficult to reach populations. These are described in further detail in Chapter 3 of this report.

The WHO Regional Strategy

To assist with the strategic implementation of this strategy, WHO have called out all the regions: Africa, America, South-East Asia, Europe, Eastern Mediterranean and Western Pacific¹⁰² to eliminate HCV as major public health threat. The Western Pacific bloc of countries, in which Malaysia is categorised,¹⁰³ has the highest number of viral hepatitis-related deaths per year, accounting for approximately 40% of global mortality due to hepatitis.¹⁰⁴ This translates into more than 1,500 deaths every day, approximately 48% from chronic HCV.¹⁰⁵

Realising this, WHO Western Pacific Regional Office (WPRO) has drawn out an action plan targeted at the regional level to mobilise the efforts at Member States levels. It is called the Regional Action Plan for Viral Hepatitis in the Western Pacific 2016–2020, following recommendations from the first

- 91 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021 towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 27] at p. 38. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>.
- 92 IHS Markit. French gov proposes 'universal' access to new HCV medicine. [Internet]. HIS Markit; 2016 May 26. [cited 2016 Nov 25] Available from: <https://www.ihs.com/country-industry-forecasting.html?ID=10659114512>
- 93 Bouscaillou J, Camet A, Forette C, Gaudino A, Gay B, Grillon C, Luhmann N. Dying at these Prices HCV .Map Crowd; [Internet] 2016 July. [cited 2016 Oct 18] p.18. Available from: http://mapcrowd.org/public/pdf/EN_mapCrowd_Report2.pdf
- 94 Bouscaillou J, Camet A, Forette C, Gaudino A, Gay B, Grillon C, Luhmann N. Dying at these Prices HCV .Map Crowd; [Internet] 2016 July. [cited 2016 Oct 18] p.18. Available from: http://mapcrowd.org/public/pdf/EN_mapCrowd_Report2.pdf
- 95 Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, Hatzakis A, Prins M, Vickerman P, Lazarus JV, Hope VD. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: A systematic review of data for scaling up treatment and prevention. PLoS one. [Internet]. 2014 Jul 28 [cited 2016 Nov 25]; 9(7):e103345. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4113410/>
- 96 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 47. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>
- 97 Ibid at p. 47. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>
- 98 DNDi [Internet]. International. Press release, Clinical Research Malaysia and the Drugs for Neglected Diseases initiative sign agreement to launch clinical studies for a public health approach to hepatitis C in Malaysia; 2016 Jan [cited 2016 Oct 18]. Available from: <http://www.dndi.org/2016/media-centre/press-releases/mou-malaysia-hepatitis-c/>
- 99 Ibid
- 100 Ibid
- 101 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 47. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>
- 102 World Health Organization: Global Burden of Disease Regions used for WHO CHOICE Analyses [Internet] WHO; 2016 [cited 2016 Oct 16]. Available from: <http://www.who.int/about/regions/en/>
- 103 World Health Organization: Global Burden of Disease Regions used for WHO CHOICE Analyses [Internet] WHO; 2016 [cited 2016 Oct 16]. Available from: <http://www.who.int/about/regions/en/>
- *Countries in Western Pacific Region: Australia, Brunei Darussalam, Japan, New Zealand, Singapore, Cambodia, China, Cook Islands Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands Micronesia, Federated States of Mongolia Nauru, Niue, Palau Papua New Guinea Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam
- 104 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region. 2016 [Internet]. 2015 Oct [cited 2016 Oct 18]. . at pV .Available from: : <http://www.wpro.who.int/hepatitis/resource/features/rapvh/en/>
- 105 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region [Internet]. 2015 Oct [cited 2016 Oct 18] at p.1. Available from: <http://www.wpro.who.int/hepatitis/resource/features/rapvh/en/>

Meeting of the Informal Expert Working Group on Surveillance Prevention, and Management of Viral Hepatitis in the Western Pacific Region in Manila, Philippines, in April 2014. The Regional Plan was approved and endorsed by Member States in 66th WHO Regional Committee in October 2016. The Regional Plan, targeted at Ministries of Health, policy-makers, non-governmental organisations, and others, provides a systematic approach to priority areas for countries to focus on towards elimination. There are five (5) priority areas of actions, which correspond to global strategic directions outlined in the WPRO Strategy, including evidence informed policy guiding a comprehensive and coordinated response and stopping transmission (see Table 3).

Both work hand in hand to ensure services and interventions are received by HCV patients, identify measures that can be taken to ensure and improve the quality of services and programmes, propose strategies to minimise the financial burden for patients who need the services and formulate ways on how coverage service can be expanded to include the marginalised HCV patients, especially those co-infected with HIV. This alignment is very essential to meet the complex challenges of preventing, diagnosing, and treating HCV in rapidly evolving contexts.

Priority area 2 in the Regional Plan identifies national-level policy as the most effective instrument for affecting change at the population level,¹⁰⁸ further cementing the urgency for a Malaysian national hepatitis plan. Developed countries have led the way with domestic policy on viral hepatitis. In 2014, France provided treatment for persons infected with HCV¹⁰⁹ despite the high cost at €41,000¹¹⁰ (MYR 187,770), with treatments being reimbursable through French's national security plan.¹¹¹ In Scotland, a national hepatitis C plan was launched in 2006,¹¹² and continued to be carried out via the Scottish Government Sexual Health and Blood Borne Virus Framework 2011-15. Via this national plan, sofosbuvir is funded in the country for relapse patients at the price of £37,000 (MYR 188, 994) per course.¹¹³ The Scottish Medicines Consortium accepted sofosbuvir because it 'addresses an unmet treatment need'.¹¹⁴ At time of writing, pegylated interferon alpha, ribavirin and simeprevir is the standard treatment for HCV patients in Scotland.¹¹⁵

In the years following the national plan, the number of new HCV infections decreased from 1,500 in 2007 to 700 in 2013.¹¹⁶ This is mainly due to several factors such as identification of HCV as a major public health threat, adequate funding tied to strict project targets on hepatitis testing and treatment and collective bargaining for HCV medication and injecting equipment at the national level.¹¹⁷

| Priority areas of actions | Corresponding strategic directions (SD) |
|---|--|
| PRIORITY AREA 1 Broad-based advocacy and awareness | SD1. Strategic information for focus and accountability |
| PRIORITY AREA 2 Evidence-informed policy guiding a comprehensive and coordinated hepatitis response | SD1. Strategic information for focus and accountability SD2. Interventions for impact SD4. Financing for sustainability |
| PRIORITY AREA 3 Data supporting the hepatitis response | SD1. Strategic information for focus and accountability |
| PRIORITY AREA 4 Stopping transmission | SD3. Delivering for equity SD4. Financing for sustainability SD5. Innovation for acceleration |
| PRIORITY AREA 5 An accessible and effective treatment cascade ¹⁰⁶ | SD3. Delivering for equity SD4. Financing for sustainability SD5. Innovation for acceleratio |

Table 2.3: Alignment of the Regional Action Plan for Viral Hepatitis in the Western Pacific priority areas with the Global Health Sector Strategy for Viral Hepatitis strategic direction.¹⁰⁷

106 A cascade is a succession of steps in a process, each of which triggers or initiates the next stage.

107 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region [Internet]. 2015 Oct [cited 2016 Oct 18] at p.5. Available from: <http://www.wpro.who.int/hepatitis/resource/features/rapvh/en/>

108 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region [Internet]. 2015 Oct [cited 2016 Oct 18] at p.11. Available from: <http://www.wpro.who.int/hepatitis/resource/features/rapvh/en/>

109 Bouscaillou J, Camet A, Forette C, Gaudino A, Gay B, Grillon C, Luhmann N. Dying at these Prices HCV .Map Crowd;[Internet] 2016 July. [cited 2016 Oct 18] p.18. Available from: http://mapcrowd.org/public/pdf/EN_mapCrowd_Report2.pdf

110 Alcorn K. France to provide universal access to hepatitis C treatment: Nam AIDS Map [Internet]. 2016 June 02 [cited 2016 15 Oct]. Available from: <http://www.aidsmap.com/France-to-provide-universal-access-to-hepatitis-Ctreatment/page/3060907/>

111 Bouscaillou J, Camet A, Forette C, Gaudino A, Gay B, Grillon C, Luhmann N. Dying at these Prices HCV. Map Crowd; [Internet] 2016 July. [cited 2016 Oct 18] p.18. Available from: http://mapcrowd.org/public/pdf/EN_mapCrowd_Report2.pdf 112 Hepatitis C action plan for Scotland: Phase 1: September 2006-August 2008. NHS Scotland, Scottish Executive: Edinburgh [Internet]. 2006 [cited 2016 Oct 31]. Available from: <http://www.gov.scot/Resource/Doc/148746/0039553.pdf>

113 Adams B. Sovaldi hurdles first drug pricing barrier: Pharamafile [Internet]. 2014 June 10. [cited 2016 Oct 25] Available from: <http://www.pharmafile.com/news/187624/sovaldi-hurdles-first-drug-pricing-barrier>

114 Scotland. Hepatitis C drug Sofosbuvir approved for use on NHS: BBC News. 2014 June 9. [cited 2016 Oct 26] Available from:<http://www.bbc.com/news/uk-scotland-27762181>

115 Healthcare Improvement Scotland. National Clinical Guidelines for the Treatment of HCV in Adults. National Services Scotland [Internet]. 2015 August [cited 2016 Oct 27]. p.4. Available from: <http://www.hps.scot.nhs.uk/resourcedocument.aspx?resourceid=1598>

116 Scottish Government. Viral Hepatitis. Sexual Health & Blood Borne Virus Framework 2015-2020 Update [Internet].2015 August 31[cited 2016 Nov 25]. Available from: <http://www.gov.scot/Publications/2015/09/5740/7>

117 Wylie L, Hutchinson S, Liddell D, Rowan N. The successful implementation of Scotland's Hepatitis C Action Plan: what can other European stakeholders learn from the experience? A Scottish voluntary sector perspective. BMC infectious diseases. BMC Infectious Disease. [Internet] 2014 Sep 19 [cited 2016 Nov 25];14(Suppl 6):S7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4178623/>

The fourth priority action in the Regional Plan focuses on stopping transmissions of HCV in vulnerable areas such as public health settings and among people who inject drugs (PWID)¹¹⁸ and recommends ‘full participation in harm reduction interventions’ to reduce HCV incidence.¹¹⁹ Given Malaysia’s extensive coverage of needle-and-syringe exchange programs, methadone centres, and outreach of these programs, there is a real opportunity in optimising existing public health infrastructure. In addition to scaling up availability of HCV rapid test kits in these facilities, this could also be done by increasing capacity of outreach workers to link into care.

Given that Malaysia is a middle-income country, examples from other middle-income countries may be useful in designing the way forward. Some middle-income countries already have concrete national strategies for elimination, and have negotiated substantial price reductions that have enabled treatment plans previously thought impossible. Georgia, one of the several states in Eastern Europe with high prevalence of HCV due to injecting drug use,¹²⁰ has worked with Gilead Sciences (manufacturer of sofosbuvir) and US Center for Disease Control and Prevention (CDC)¹²¹ to provide 5,000 free courses of sofosbuvir intended for people with severe liver fibrosis.¹²² By April 2016, a total of 27,392 HCV infected persons enrolled for the programme, 8,448 patients started on treatment, and 5,850 had already completed treatment.¹²³

Georgia’s HCV scenario is similar to Malaysia where more than 59% of the HCV cases are attributed to injection drug use.¹²⁴ Malaysia’s Intervention Note on Viral Hepatitis in the 66th Session of the WPRO Regional Committee Meeting in October 2015 has commended the Regional Plan, which focuses on the move to eliminate HCV by focusing on the population at-risk such as PWID.¹²⁵ Malaysia also calls for the need for global intervention to reduce the cost and safeguard the accessibility of the treatment in these countries.¹²⁶ The WHO estimates the cost of implementing the strategy in low- and middle-income countries for 2016–2021 would be US\$11.9 billion, with a peak at US\$ 4.1 billion for the year 2021.¹²⁷ The principal drivers of cost are testing and treatment for hepatitis B and C. This would prevent 7.1 million deaths between 2015 and 2030.¹²⁸

In conclusion, the WHO Global Strategy and WPRO Regional Plan contains several key priority actions and strategies that will be instructive and necessary for Malaysia to implement in the way forward, including those on equitable access, high impact interventions and innovation to achieve the global targets on HCV.¹²⁹

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- 118 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ; [page 24]. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf
- 119 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ; [page 24]. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf
- 120 Mitruka K, Tsertsvadze T, Butsashvili M, Gamkrelidze A, Sabelashvili P, Adamia E, Chokheli M, Drobeniuc J, Hagan L, Harris AM, Jiqia T. Launch of a nationwide hepatitis C elimination program—Georgia, [Internet] April 2015. *MMWR Morb Mortal Wkly Rep* [cited 2016] Oct 15];64:753-Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26203628>
- 121 Hirschler B. Gilead uses Georgia as free-drug testbed for hepatitis C elimination. Reuters [Internet]. 2015 Apr 22 [cited 2016 Oct 15]. Available from: <http://www.reuters.com/article/us-health-hepatitis-gilead-georgiaidUSKBN0ND1XU20150422>
- 122 Hirschler B. Gilead uses Georgia as free-drug testbed for hepatitis C elimination. Reuters [Internet]. 2015 Apr 22 [cited 2016 Oct 15]. Available from: <http://www.reuters.com/article/us-health-hepatitis-gilead-georgiaidUSKBN0ND1XU20150422>
- 123 Gvinjilia L, Nasrullah M, Sergeenko D, Tsertsvadze T, Kamkamidze G, Butsashvili M, Gamkrelidze A, Imnadze P& others. National Progress Toward Hepatitis C Elimination — Georgia, 2015–2016. *Morbidity & Mortality Weekly Reports*. Centers for Disease Control & Prevention. [Internet] 2016 Oct 21; [cited 2016 Nov 25]; 65(41);1132–1135. Available from: <http://www.cdc.gov/mmwr/volumes/65/wr/mm6541a2.htm#contribAff>
- 124 McDonald SA, Mohamed R, Dahlui M, Naning H, Kamarulzaman A. Bridging the data gaps in the epidemiology of hepatitis C virus infection in Malaysia using multi-parameter evidence synthesis. *BMC infectious diseases*. 2014 Nov 7; [cited 2016 Oct 18]14(1):1. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25377240>
- 125 Malaysia’s Intervention Note on Viral Hepatitis in the 66th Session of the WPRO Regional Committee Meeting in October 2015. [Internet]. 2015 Oct 16 [cited 2016 Oct 15]. Available from: <https://kpkeshatan.com/2015/10/13/malaysiasintervention-note-on-viral-hepatitis-at-the-66th-session-of-wpro-regional-committee-meeting-12-16th-oct-2015/>
- 126 Malaysia’s Intervention Note on Viral Hepatitis in the 66th Session of the WPRO Regional Committee Meeting in October 2015. [Internet]. 2015 Oct 16 [cited 2016 Oct 15]. Available from: <https://kpkeshatan.com/2015/10/13/malaysiasintervention-note-on-viral-hepatitis-at-the-66th-session-of-wpro-regional-committee-meeting-12-16th-oct-2015/>
- 127 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ; at p.6. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf
- 128 World Health Organization. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. [Internet]. [cited 2016 Oct 18] ; at p.6. Available from: http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf
- 129 World Health Organization. Regional action plan for viral hepatitis in the Western Pacific 2016-2020: a priority action plan for awareness, surveillance, prevention, and treatment of viral hepatitis in the Western Pacific Region [Internet]. 2015 Oct [cited 2016 Oct 18] at p.51. Available from: <http://www.wpro.who.int/hepatitis/resource/features/rapvh/en/>

Chapter 3

Scaling-up Diagnostics in Malaysia

Fifa Rahman

At the baseline of diagnosing HCV at 2,105 persons per year, Malaysia will not achieve the WHO viral hepatitis diagnostics targets. Several other barriers exist, i.e. that infrastructure in major hospitals does not allow for doctors to confirm HCV infection with sensitive molecular methods (although core antigen is available), that there have been federal budget cuts on the purchase of drugs, vaccines, consumables and reagents, and that the current diagnostics pathway is unduly complex. This chapter discusses current coverage of HCV diagnostics in Malaysia, the cost burden on patients, and the way forward.

Kini, Malaysia mendiagnos 2,105 orang sebagai menghidap HCV setiap tahun. Pada kadar ini, Malaysia tidak akan mencapai sasaran Petubuhan Kesihatan Sedunia (WHO). Beberapa halangan lain juga wujud, iaitu bahawa tahap infrastruktur di hospital-hospital utama tidak membenarkan doktor untuk mengesahkan jangkitan HCV dengan kaedah molekul sensitif, terdapat pemotongan belanjawan persekutuan berkenaan pembelian ubat-ubatan, vaksin, dan reagen, dan bahawa laluan diagnostik semasa adalah terlalu kompleks. Bab ini membincangkan liputan semasa ujian HCV di Malaysia, beban kos pada pesakit, dan cara mengatasi masalah-masalah ini.

The current state of HCV diagnostics in Malaysia

A substantial proportion of patients with chronic hepatitis worldwide are still unaware of their condition, and this is a major barrier to HCV elimination.¹³⁰ WHO targets state that Malaysia must have diagnosed 30% of people living with HCV by 2020.¹³¹ Depending on what prevalence estimates we rely on, this means that 53,312 - 156,805 HCV seropositive individuals must be diagnosed by 2020. There is no publicly available data on the number of persons diagnosed with HCV, although an upcoming study by Rosmawati and Razavi (2017)¹³² states that 28,826 persons have been diagnosed screening in 1993, and Min 2,108 persons¹³³ were diagnosed total diagnosis to 30,932 per diagnose at the current yearly targets, even at the lower three

| | 2013 |
|-----------------------------|----------------------|
| Number of persons diagnosed | 2,011 ¹³³ |

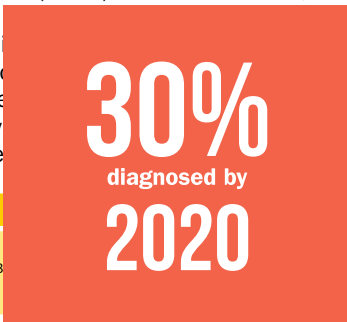


Table 3.1: Number of persons diagnosed in Malaysia (2013-2015)

McDonald et al (2014) describe that while HCV antibody testing occurs in blood donor sites, opioid substitution therapy, and hospital settings, among others, screening in Malaysia can only be considered comprehensive for prospective blood donors.¹³⁷ HCV screening also does not routinely occur as part of antenatal screening.¹³⁸ Barriers to diagnosis include budgetary inadequacies, which led to a temporary halt in laboratory tests in 2016, as laboratories were unable to purchase the necessary chemical reagents.¹³⁹ While MOH is evaluating their financial shortcomings,¹⁴⁰ monumental cuts to the national health budget¹⁴¹ raise questions as to how scale up of HCV diagnostics will occur. The 2017 budget, tabled by the Prime Minister on 21st October 2016, saw an overall increase in the health budget (by RM2 billion), but a reduction of RM600m (USD \$142.92 million) for the supply of drugs, consumables, vaccines, and reagents.¹⁴²

| | 2016 | 2017 |
|--|----------------------------|----------------------------|
| Budget allocated for supply of drugs, consumables, vaccines, and reagents (RM) | 4.6 billion ¹⁴³ | 4.0 billion ¹⁴⁴ |

130 EASL Recommendations on Treatment of Hepatitis C 2016. Hepatology (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001>. [Internet]. [cited 2016 Nov 1]. Available from: <http://www.easl.eu/medias/cpg/HCV2016/Englishreport.pdf>

131 WHO-Western Pacific Region (WPRO). Regional action plan for viral hepatitis in the Western Pacific 2016-2020. [Internet] 2016 [cited 2016 Oct 25] at 7. Available from: http://iris.wpro.who.int/bitstream/handle/10665.1/13141/97892906177617_eng.pdf

132 Rosmawati M, Razavi H (upcoming) 2017.

133 Health indicators 2016. Health Informatics Centre, Ministry of Health, Malaysia [cited 2016 Nov 2].

134 Health indicators 2014. Health Informatics Centre, Ministry of Health, Malaysia. [cited 2016 Oct 31]. Available from: <http://www.moh.gov.my/english.php/pages/view/56>

135 Health Indicators 2015. Health Informatics Centre, Ministry of Health, Malaysia. [cited 2016 Oct 31]. Available from: http://vlib.moh.gov.my/cms/documentsstorage/com.tms.cms.document.Document_32d2008b-a0188549-72493700-66672aca/Health%20Indicators%20%202015.pdf

136 Health indicators 2016. Health Informatics Centre, Ministry of Health, Malaysia [cited 2016 Nov 2].

137 McDonald SA, Mohamed R, Dahlui M et al. Bridging the data gaps in the epidemiology of hepatitis C virus infection in Malaysia using multi-parameter evidence synthesis. BMC Infectious Diseases 2014; 14: 564

138 Profiles. Gribbles Pathology. [Internet]. [cited 2016 Oct 27]. Available from: <http://www.gribbles.com.my/index.cfm?&menuid=49>

139 Khoo V-J. Lack of funds leads to suspension of clinical laboratory tests in Malaysian hospitals. MIMS [Internet]. 2016 Oct 9 [cited 2016 Oct 26]. Available from: <http://today.mims.com/topic/lack-of-funds-leads-to-suspension-of-clinical-laboratorytests-in-malaysian-hospitals>

140 Khoo V-J. Lack of funds leads to suspension of clinical laboratory tests in Malaysian hospitals. MIMS [Internet]. 2016 Oct 9 [cited 2016 Oct 26]. Available from: <http://today.mims.com/topic/lack-of-funds-leads-to-suspension-of-clinical-laboratorytests-in-malaysian-hospitals>

141 Aziz F. Health ministry faces budget cut of between RM250m and RM300m. New Straits Times Online [newspaper on the Internet]. 2016 Jan 13 [cited 2016 Oct 31]. Available from: <http://www.nst.com.my/news/2016/01/122006/health-ministryfaces-budget-cut-between-rm250m-and-rm300m>

142 2017 budget: ensuring unity and economic growth. Ministry of Finance [Internet]. [cited 2016 Oct 31]. Available from: http://www.treasury.gov.my/pdf/budget/speech/touchpoints_budget_2017.pdf

Table 3.2: Federal budget allocation for supply of drugs, consumables, vaccines, and reagents (RM)

There has been no previous documentation of private insurance coverage for HCV. In the preparation of this report, 2 private health insurance companies were contacted by phone. Both did not provide coverage for preexisting illnesses including HCV.¹⁴⁵ In an email to the author dated 8 November 2016, however, Allianz stated that under its Medisafe policies, if HCV is contracted after the purchase of the policy, HCV diagnostics and treatment is covered.

There are a number of HCV diagnostic tests and tools, i.e.

HCV antibody tests, including rapid tests and lab-based immunoassays, HCV qualitative RNA tests,¹⁴⁶ and HCV core antigen, and pre-treatment assessment tests as well as monitoring tests i.e. “viral load” (quantitative RNA) tests, liver function tests, staging tests and genotype tests. The purpose of each of these tests are tabulated below:

HCV diagnostic tests/
pre-treatment assessment tests

| | |
|---|---|
| Rapid HCV antibody (serology) tests | Rapid tests detect HCV antibodies in fingerstick and venipuncture whole blood, as well as other sample types such as oral fluid, plasma and serum, in a short space of time, for example, 20 minutes. Someone who tests positive with these tests is only preliminarily positive and must undergo further testing. |
| Lab-based HCV antibody (serology) tests | These tests detect antibodies to HCV in the blood, however it cannot tell the difference between a new (acute) infection, ¹⁴⁷ a long-term (chronic) infection, or whether the infection has resolved after spontaneous cure or previous treatment, therefore a virological confirmatory test is needed. A positive result simply means that the individual has been infected or exposed at some point in time. ¹⁴⁸ The most common type of HCV antibody test is the enzyme immunoassay (EIA) test but chemiluminescent options also exist. ¹⁴⁹ |
| HCV RNA tests | These tests measure the amount of hepatitis C virus in the blood. They are needed to distinguish people who have spontaneously cleared the virus (i.e. those whose immune systems clear it) from those who have chronic infection. ¹⁵⁰ There are qualitative and quantitative (viral load) RNA tests. For treatment with DAAs, only a qualitative result is necessary as no on-treatment viral load count is necessary. |
| Liver function tests (LFT) | These tests provide a gauge of how damaged the liver cells are. For people with hepatitis C, the enzyme Alanine Aminotransferase (ALT) is one of the most relevant enzymes measured by an LFT. ¹⁵¹ ALT is released into the blood when liver cells are inflamed. |
| Genotype tests | These tests detect the genetic variances in the hepatitis C virus. These genetic variances (Genotype 1-6) determine the ease of treatment, and at present, the type of medication. This test will not be required with pan-genotypic DAA combination treatment. |
| Staging of fibrosis and cirrhosis | HCV progresses in stages, and influences the type and duration of treatment that needs to be given. The more fibrosis and cirrhosis, the more complex treatment is. The WHO recommends that these be done with aminotransferase/platelet ratio index (APRI) or FIB4 for resource poor-settings. ¹⁵² |

Table 3.3: Types of HCV Diagnostic Test

The recommended sequence of the diagnostic tests is prescribed by, among others, the Centre for Disease Control in the U.S., the World Health Organisation (WHO)¹⁵³ and the European Association for the Study of the Liver (EASL). EASL guidelines are seen as the gold standard for diagnosis and treatment in the field, as they are compiled by the world’s leading liver specialists, and are

143 2017 budget: ensuring unity and economic growth. Ministry of Finance [Internet]. [cited 2016 Oct 31]. Available from: http://www.treasury.gov.my/pdf/budget/speech/touchpoints_budget_2017.pdf

144 2016 budget. Ministry of Finance, Malaysia [Internet]. 2015 [cited 2016 Oct 31] at 36. Available from: http://www.bnm.gov.my/files/Budget_Speech_2016.pdf

145 Phone conversation between Fifa Rahman, Manager, HCV Access & Affordability, and AIA and AIG. 2016 Nov 1.

146 ribonucleic acid

147 Early acute infections are pre-antibody response and require detection by virological testing.

148 Hepatitis C: what to expect when getting tested. Centre for Disease Control (CDC) [Internet]. [cited 2016 Oct 31]. Available from: <https://www.cdc.gov/hepatitis/hcv/pdfs/hepcgettingtested.pdf>

149 Laboratory tests and hepatitis C. National Hepatitis C Program Office: U.S. Department of Veteran’s Affairs. [cited 2016 Nov 1]. Available from: <http://www.hepatitis.va.gov/provider/reviews/laboratory-tests.asp>

150 Global report on access to hepatitis C treatment: focus on overcoming barriers [Internet]. Geneva: World Health Organisation (WHO); 2016 Oct [cited 2016 Oct 31] at 10. Available from: <http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1>

151 Tests and hep c. Hepatitis Australia [Internet]. [cited 2016 Nov 1]. Available from: <http://www.hepatitisaustralia.com/hepatitis-c-facts/tests-for-hep-c>

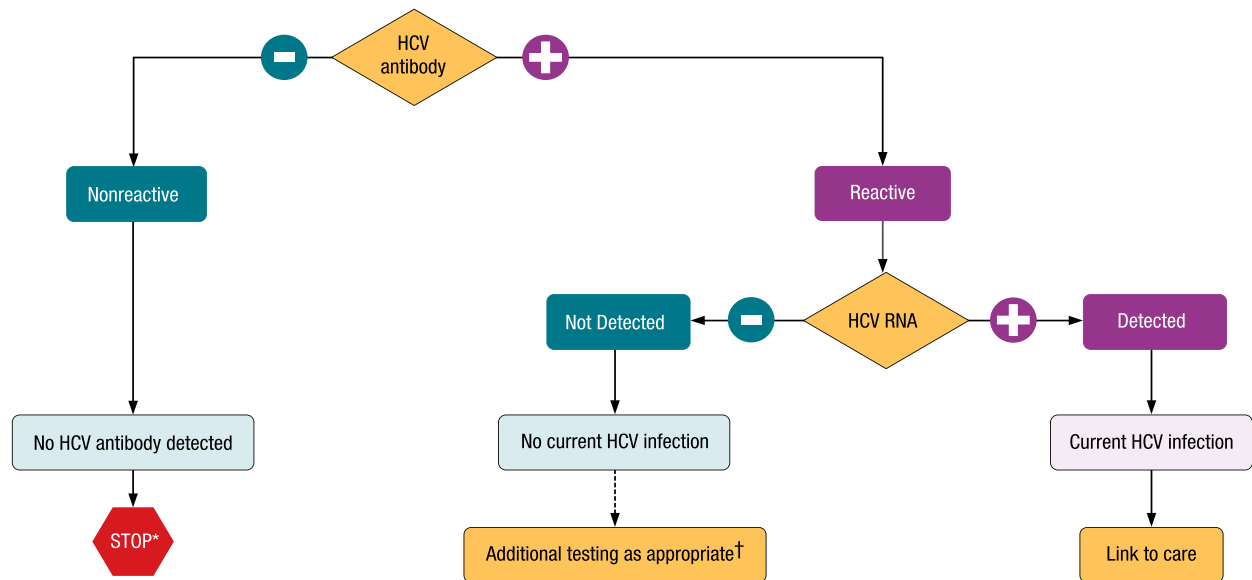
152 The WHO recommends that aminotransferase/platelet ratio index (APRI) or FIB4 be used for the assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or Fibrotest. Guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organisation: Geneva [Internet]. 2014 Apr [cited 2016 Nov 28] at 56. Available from: http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

practiced by Malaysian hepatologists and gastroenterologists. Both recommend a two-step test for identifying HCV infection, i.e. the HCV antibody test as the first step and the HCV RNA test for confirmation of current HCV infection. In October 2016, the WHO described the two-step process as ‘a challenge’¹⁵⁴ due to the fact that patients in many low- and middle-income countries (LMICs) have to bear the costs themselves. As discussed in Chapter 2 of this report, the WHO also recommends that national viral hepatitis plans must incorporate diagnostics that they do not place a substantial financial burden on patients.¹⁵⁵

diagnostic tests to facilitate anti-HCV screening and improve access to care.¹⁵⁷ The most recent WHO guidelines (Nov 2016) recommend the use of dried blood spot (DBS) tests in resource-poor settings to facilitate uptake of testing and linkage into care.¹⁵⁸

In-vitro diagnostics (IVD) are registered in Malaysia under the Medical Device Act 2012, and must be subject to a ‘conformity assessment’ prior to approval for marketing,¹⁵⁹ which requires that the manufacturer attests that the IVD medical device complies with all applicable Essential Principles for Safety and Performance as documented in a written ‘Declaration of Conformity’ (DOC).¹⁶⁰ These procedures are lodged with the Medical Device Authority (MDA) under the Ministry of Health, who decides what IVDs enter the market. In a teleconversation with the MDA on the 28th of November 2016, they confirmed that approval was mainly decided in reference to the Global Harmonisation Task Force, now known as the International

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection



* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.
 † To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
 Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. *MMWR* 2013;62(18).

Figure 3.1: CDC HCV Diagnosis Algorithm ¹⁵⁶

While EASL recommends the anti-HCV antibody test as the first-line diagnostic test, it also strongly recommends the use of rapid

153 Guidelines on hepatitis B and C testing. World Health Organisation: Geneva [Internet]. 2016 Nov [cited 2016 Nov 28] at 14. Available from: <http://www.who.int/hepatitis/publications/hepatitis-testing-recommendation-policy/en/>

154 Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: World Health Organisation [Internet]. 2016 Oct [cited 2016 Oct 31]. Available from: <http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1>

155 World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. [Internet]. 2016 May [cited 2016 Oct 24] at p. 14. Available from: <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>

156 Recommended testing sequence for identifying current hepatitis C virus (HCV) infection. Centres for Disease Control, U.S. Department of Health and Human Services [Internet]. [cited 2016 Nov 1]. Available from: http://www.cdc.gov/hepatitis/hcv/PDFs/hcv_flow.pdf

157 European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. *Journal of Hepatology* 2015; 63:199-236 at p. 200.

158 Guidelines on hepatitis B and C testing. World Health Organisation: Geneva [Internet]. 2016 Nov [cited 2016 Nov 28] at 6. Available from: <http://www.who.int/hepatitis/publications/hepatitis-testing-recommendation-policy/en/>

159 Medical Devices Act 2012 (Act 737), s7160 Principles of conformity assessment for IVD medical devices. Medical Devices Authority, Ministry of Health Malaysia: Putrajaya. [cited 2016 Nov 28]. Available from: http://www.mdb.gov.my/mdb/documents/conformity_assessment_for_ivd.pdf

160 Principles of conformity assessment for IVD medical devices. Medical Devices Authority, Ministry of Health Malaysia: Putrajaya. [cited 2016 Nov 28]. Available from: http://www.mdb.gov.my/mdb/documents/conformity_assessment_for_ivd.pdf

Medical Device Regulators Forum.

There are several rapid tests available in the Malaysian market, for example the Alere Biotest (pictured) and ABON rapid tests. These tests are offered to patients at RM25-30 (USD \$5.60-6.70) per test in clinical settings, but are estimated to cost one-fifth of this price. It is a whole blood fingerstick test, and can be offered in NGO settings by trained staff. In an interview conducted for this report, Alere Malaysia stated that their tests were mainly available in haemodialysis units of public hospitals, laboratories of some private hospitals, and in NGO settings. The Biotest tests are WHO prequalified.

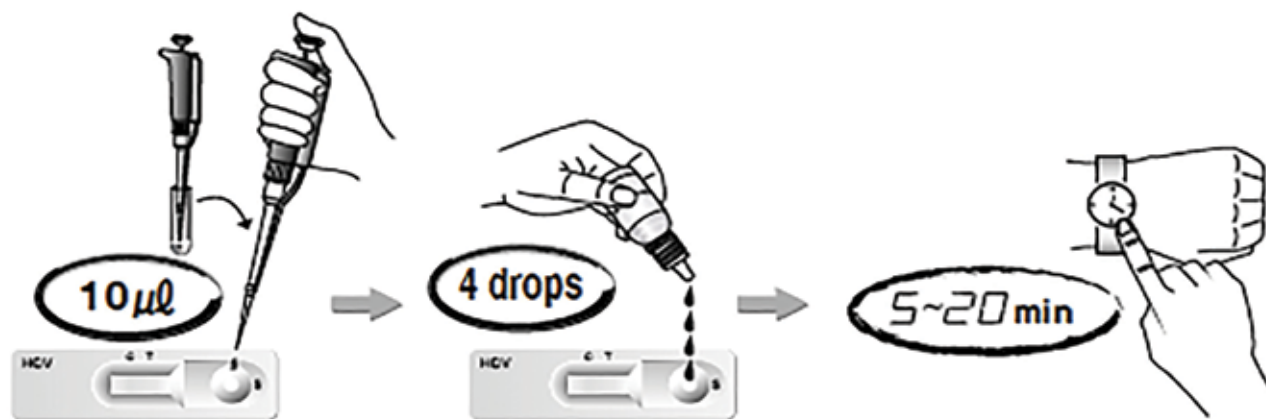


Figure 3.2: SD Biotest Rapid Test

HCV antibody tests are available in government hospitals and community health clinics, private hospitals and also in GP settings. In government settings, they are provided for free. They are predominantly supplied by Abbott Diagnostics and Roche Diagnostics, with 440,000 HCV antibody tests sold by the former in January-October 2016,¹⁶¹ and approximately 300,000 (Elecsys anti-HCV II) sold by the latter per year.¹⁶² The Elecsys anti-HCV tests cost RM8.50 (USD \$1.95) per test.

Qualitative and quantitative HCV RNA (viral load) testing

HCV RNA tests must be conducted to confirm active HCV infection.¹⁶³ This is because 20-30% of patients who test positive with the HCV antibody test have actually cleared the virus and do not have active chronic infection.¹⁶⁴ HCV RNA tests are not available for free in public health system. Patient testimony collected in the preparation of this report indicate that prices vary in different states, with the patients reporting paying as low as RM400 (USD \$95.30) in the state of Terengganu and RM530 (USD \$126.28) in the state of Kelantan. Cost price of HCV RNA tests have been reported

internationally as ranging between USD \$13-35 (RM58-156) per result.¹⁶⁵ Based on this, Malaysian market prices are very high, and governments may find value in renegotiating market prices. Anecdotes indicate that price differences also account for logistical issues, such as the distance of the hospital from laboratory facilities.

HCV RNA tests are conducted by extracting whole blood via a syringe. The sample is then centrifuged, plasma/serum extracted with pipettes, and the sample is inserted either into a lab-based platform or into a cartridge containing reagents. This plate or cartridge is then inserted into machines for analysis, for example the cartridge-based GeneXpert

machines (produced by Cepheid) [figure 3], or the lab-based cobas machines (produced by Roche Diagnostics) [figure 4]. There are a number of different machines that can be used for analysis, and these may be found in the 2015 Doctors Without Borders report, 'Putting HIV and HCV to the Test'.¹⁶⁶ For the purposes of this report, we will be comparing two platforms that are available in Malaysian hospitals. Keeping in mind that the choice of instrument is dependent on a number of different factors, such as price and tier of healthcare system, different instruments may be suited to different contexts in the domestic healthcare scene.

According to the 2016 EASL recommendations, HCV RNA detection and quantification should be made by a sensitive assay with a lower limit of detection of ≤ 15 IU/ml.¹⁶⁷ Both these machines satisfy these requirements. HCV RNA results can be obtained after 100 minutes¹⁶⁸ (GeneXpert) and 60 minutes (Cobas).

161 Lim YK, Marketing Manager, Abbott Diagnostics Division. Sales data – HCV antibody. Email to Fifi Rahman (author) 2016 Oct 26 [cited 2016 Nov 1]. 5-10% were used in laboratories for calibration and quality control.

162 Low A, Senior Product Executive, Roche Diagnostic

163 EASL Recommendations on Treatment of Hepatitis C 2016. *Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001>

164 Hepatitis C: the hidden epidemic. *Médecins Sans Frontières* [Internet]. [cited 2016 Oct 2015]. Available from: http://www.msfaccess.org/sites/default/files/MSF_Access_HEP_C_Issue_Brief.pdf

165 Putting HIV and HCV to the test: a product guide for point-of-care CD4 and laboratory-based and point-of-care virological HIV and HCV tests. MSFAccess: Geneva [Internet]. 2015 Jul [cited 2016 Nov 28]. Available from: http://www.msfaccess.org/sites/default/files/HIV_HCV_Report_Diagnostic_Guide_2015.pdf

166 Ibid.

167 EASL Recommendations on Treatment of Hepatitis C 2016. *Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001>

168 Janiĕková O, Gašparoviĕ J, Štiĕgová H. Detection of hepatitis C virus in different samples with GeneXpert HCV viral load kit. *Abstracts / Journal of Clinical Virology* 70 (2015) S1–S126 at p. S88.



Figure 3.3: Cepheid GeneXpert



Figure 3.4: Roche Cobas 6000

The Roche cobas machines are more widely available, with 160 machines nationwide.¹⁶⁹ 10-15 of these machines are in East Malaysia (Sabah and Sarawak). The Cobas 6000 series machine [figure 4], which is contained in private laboratories and hospitals, can perform 170 immunoassay tests per hour. The machine requires an individual with a Diploma in Medical Laboratory Technology to operate.

Furthermore pros and cons should be listed because choice of instrument can be based on many things e.g. price, throughput, tier of healthcare system, patient access, accuracy, sample type etc.

The TaqMan analyser, similarly to all PCR-based tests, works by ‘amplifying’ small sections of copy DNA transcribed from HCV RNA until there are enough to analyse. There are three clear steps in each cycle, and each cycle approximately doubles the amount of target DNA. This is an exponential reaction so more than one billion copies of the original or “target” DNA are generated in 30 to 40 PCR cycles.

There are about 25 GeneXpert machines in Malaysia, with 84 modules¹⁷⁰ countrywide for the insertion of cartridges. Of this figure, GeneXpert (4-module) systems are available in 14 public hospitals across 10 states in Malaysia.

| States (alphabetical order) | Hospitals |
|-----------------------------|---|
| Johor | Hospital Sultanah Aminah |
| Kedah | Hospital Sultan Abdul Halim, Sungai Petani |
| Kelantan | Hospital Raja Perempuan Zainab II, Kota Bharu |
| Kuala Lumpur | Institut Perubatan Respiratori Malaysia (Institute of Respiratory Medicine) |
| Penang | Hospital Pulau Pinang |
| Perak | Hospital Raja Permaisuri Bainun, Ipoh |
| Sabah | Hospital Queen Elizabeth, Kota Kinabalu Hospital Tawau, Tawau |
| Sarawak | Hospital Umum Sarawak (Sarawak General Hospital), Kuching Hospital Sibu, Sibu Klinik Kesihatan Sandakan, Sandakan |
| Selangor | Hospital Sungai Buloh Hospital Tengku Ampuan Rahimah, Klang |
| Terengganu | Hospital Sultanah Nur Zahirah, Kuala Terengganu |

Table 3.4: GeneXpert systems available in the Malaysian public health system¹⁷¹

GeneXpert Dx cartridges hold samples and reagents for processing, and they are disposable¹⁷² and meant for single-use.¹⁷³ A deal brokered by FIND (an international non-profit focused on diagnostics for poverty-related diseases) means that Malaysia can procure Xpert cartridges at USD \$17.10 (RM71.76) per unit,¹⁷⁴ and can purchase the GeneXpert IV module with desktop (machine) for USD \$17,000 (RM 71,349).

A smaller machine will be launched by Cepheid in 2017 called the Omni [figure 5], which is portable, handheld, and relatively affordable at the targeted price of USD \$3000 (RM 12,591). Its mobility means that the machine can be brought to the patient. Given that the differential prices of HCV RNA tests across Malaysia may be due to logistics costs in transporting samples to laboratories, bringing the machine to patients could reduce the costs of HCV RNA tests.



Figure 3.5: Cepheid Omni portable system

169 Low A, Senior Product Executive, Roche Diagnostic (M) Sdn Bhd. Re: HCV national situational report. Email to Fifa Rahman (author) 2016 Nov 10 [cited 2016 Nov 11].

170 WHO monitoring of Xpert MTB/RIF roll-out: Procurements of GeneXperts and Xpert MTB/RIF cartridges. World Health Organisation (WHO) [Internet] 2015 Q4 [cited 2016 Nov 2]. Available from: <http://www.who.int/tb/laboratory/xpertmap>

171 Confirmed by Bio-Focus Saintifik Sdn Bhd, Cepheid distributor in Malaysia, in an email dated 8 November 2016 [cited 2016 Nov 11].

172 However, must still be disposed of as medical waste.

173 Cepheid. [Internet]. [cited 2016 Oct 26]. Available from: <http://www.cepheid.com/us/cepheidsolutions/systems/genexpert-systems/genexpert-iv>

174 FIND-negotiated product pricing. FIND [Internet]. [cited 2016 Nov 1]. Available from: <http://www.finddx.org/pricing/>

The operation of GeneXpert machines do not require sophisticated laboratory set-ups or highly trained lab technicians. AIDSmap reports that nurses, other staff, and in the case of South Africa, even the Minister of Health,¹⁷⁵ can be trained to perform the test with GeneXpert. In Malaysia, however, GeneXpert machines are predominantly used in the TB field. Thus, while capacity exists for the scale-up of HCV RNA tests with GeneXpert, internal MOH discussions for joint use of the machines for TB diagnosis and HCV diagnosis may be needed.

| Diagnostic tests/ Assessments | Market Price (RM) |
|----------------------------------|--------------------------------|
| Anti-HCV antibody test | Free |
| HCV RNA test (at baseline) | 400 |
| Genotyping | 350 |
| Liver Function Test | Free |
| Haemoglobin and Creatinine tests | Free |
| HCV RNA test (Week 12 – SVR) | 400 |
| Total | RM 1,150 (USD \$258.27) |

Table 3.5: Types of Diagnostic Test and Market Price

Sensitive molecular methods should be the default confirmatory test as recommended by EASL.¹⁷⁶ However, in Malaysia, current practice in many places is still to confirm HCV with particle agglutination and HCV recombinant immunoblot assay (RIBA) tests, which do not necessarily show active current HCV infection. Laboratories in all major state hospitals need to be upgraded with molecular diagnostic facilities, and HCV confirmatory tests should solely be based on HCV RNA tests. There's also a great need to simplify the diagnostics algorithm to prevent the loss of patients to follow-up after the HCV antibody tests.

~Dr Tee Hoi Poh

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Genotyping

Given that international treatment guidelines (WHO and EASL) still differentiate treatments based on genotype, genotype testing is still necessary prior to treatment initiation.¹⁷⁷ However, expensive prices mean that many are unable to pay for these tests. In Malaysia, these too are not covered under the public health system. Patient testimonials taken in the production of this report indicate that depending on location throughout the country, patients can pay expect to pay anywhere from RM350-640 (USD \$80.45-152.80).¹⁷⁸

Liver function test

Liver function tests are provided for free in public hospitals. In private laboratories in Kuala Lumpur, they cost RM42 (USD \$10).

Costs and the way forward in HCV diagnostics

In the public health system, assuming the antibody test is the first line of testing, out-of-pocket expenses for HCV diagnostics and assessments carried out pre-, post-, and during treatment would cost at least RM1,950 (USD \$448.27). These costs are tabulated below:

To contextualise these prices, statistics show that rural average household income is RM3,831 (USD \$879.27) per month.¹⁷⁹ Lower income groups have been shown to spend 33.03% of their incomes on food,¹⁸⁰ leaving very little for other expenditure. Malaysian out-of-pocket health expenditure as a percentage of private expenditure is high at 78.8%.¹⁸¹ Also, as aforementioned, cost price of HCV RNA, for example, is inflated – with cost price per test result provided by the diagnostics industry at USD \$13-35 (RM58-156).¹⁸²

Conclusion

At present, the complex and expensive diagnostics pathway means that many patients are lost to follow up, which is a key barrier for elimination of HCV. These problems can be fixed, because investment in pan-genotypic DAAs would simplify the diagnostics algorithm, as among other things, it would remove the need for genotyping and staging. In terms of costs, the market price of some diagnostics are inflated, needing a disaggregated breakdown of costs and renegotiation. Infrastructure for HCV RNA testing is readily available in Malaysia in government hospitals. However, the current budget for the test will not be sufficient to support the WHO target of 30% diagnosed by 2020.

175 Smart T. GeneXpert to be rolled out as first-line diagnostic for TB in South Africa. Nam AIDSmap [Internet]. 2011 Mar 31 [cited 2016 Oct 26]. Available from: <http://www.aidsmap.com/GeneXpert-to-be-rolled-out-as-first-line-diagnostic-for-TB-in-South-Africa/page/1746803/>

176 EASL Recommendations on Treatment of Hepatitis C 2016. Hepatology (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001> at p. 2.

177 Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: World Health Organisation [Internet]. 2016 Oct [cited 2016 Oct 31]. Available from: <http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1>

178 Testimonials from patients located in Kuantan, Pahang; Taiping, Perak; and Johor Bahru, Johor.

179 Report of household income and basic amenities survey 2014: Press Release. Department of Statistics Malaysia [Internet]. 2015 Jun 22 [cited 2016 Nov 11]. Available from: <https://www.statistics.gov.my/index.php?r=column/pdfPrev&id=aHhtTHVWNVYzTFBua2dSUlBRL1Rjdz09>

180 Tey J Y-S. Household expenditure on food at home in Malaysia. [Internet] 2008 Jul 20 [cited 2016 Nov 11]. Available from: <https://mpr.ub.uni-muenchen.de/15031/>

181 Out-of-pocket health expenditure (% of private expenditure on health). The World Bank [Internet]. [cited 2016 Nov 11]. Available from: <http://data.worldbank.org/indicator/SH.XPD.OOPC.ZS?end=2014&locations=MY&start=1995&view=chart>

182 Putting HIV and HCV to the test: a product guide for point-of-care CD4 and laboratory-based and point-of-care virological HIV and HCV tests. MSFAccess: Geneva [Internet]. 2015 Jul [cited 2016 Nov 28]. Available from: http://www.msfacecess.org/sites/default/files/HIV_HCV_Report_Diagnostic_Guide_2015.pdf

CHAPTER 4

HCV treatment in Malaysia: in a time of transition and planning

Fifa Rahman and Prof Dr Rosmawati Mohamed

This chapter summarises the current treatment landscape in Malaysia and the latest recommendations from the international medical community. It is by no means to be used as a comprehensive reference for the treatment of persons living with HCV. The most recent medical evidence recommends the use of DAAs for HCV treatment, given high response rates and significantly reduced side effects. At time of writing, treatment in the public healthcare system is still pegylated interferon-ribavirin, although discussions are ongoing in the Ministry of Health on access and affordability of DAAs.

Bab ini meringkaskan landskap rawatan HCV di Malaysia dan cadangan terbaru daripada komuniti pakar perubatan antarabangsa. Ia tidak harus digunakan sebagai rujukan yang komprehensif untuk rawatan pesakit HCV. Bukti perubatan yang terkini mengesyorkan penggunaan direct-acting antivirals (DAAs) untuk rawatan HCV, memandangkan kadar tindakbalas yang tinggi dan kesan sampingan yang kurang. Pada masa penulisan, rawatan dalam sistem kesihatan awam masih menggunakan rawatan pegylated interferon-ribavirin. Namun begitu, rundingan dan perbincangan sedang dijalankan di Kementerian Kesihatan berkenaan dengan akses kepada ubatan DAA.

The basics of HCV treatment

The combination of pegylated interferon and ribavirin is the current standard regimen for the treatment of HCV regardless of genotype in Malaysia. Pegylated interferon is an injectable medication, whereas ribavirin is consumed orally, with treatment reaching up to 48 weeks depending on the genotype of the HCV infection. Side effects include flu-like symptoms, fatigue, apathy, depression (pegylated interferon) and haemolytic anaemia (ribavirin), among others.¹⁸³ Sustained virological response (SVR) is considered a cure and is defined by undetectable HCV RNA (see Chapter 3 of this report) in blood at 12 weeks (SVR12) or 24 weeks (SVR24) post treatment.¹⁸⁴ SVR rates are lower with pegylated interferon-ribavirin, particularly for genotype 1, as compared to the new direct-acting antivirals (DAAs). The combination of DAAs, on the other hand, are all consumed orally for as short as 8 weeks with cure rates approaching 100%, with very few side effects, if any. In Malaysia, access to the DAAs are limited. Recent literature has suggested that the HCV cascade not end with treatment, but rather with interventions to prevent reinfection.¹⁸⁵

HCV treatment in Malaysia thus far

In Malaysia, about 500 persons a year are treated for HCV (Table 1) with pegylated interferon-ribavirin. According to targets set by the WHO Global Health Sector Strategy for viral hepatitis and Western Pacific region targets, both screening and treatment will need to be scaled up drastically from now to reach the 2030 elimination targets and the interim targets in 2020.

| Year | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---------------------------|------|------|------|------|------|------|
| Number of persons treated | 450 | 480 | 645 | 536 | 554 | 544 |

Table 4.1: Number of persons treated for HCV (2009-2014)

Who should be treated?

The European Association for the Study of the Liver (EASL) recommendations on treatment of Hepatitis C, has defined who *must be considered* for therapy, who *must be treated without delay*, and for whom treatment is *not recommended*. These are tabulated below.

| | |
|--|--|
| Must be considered for therapy | <ul style="list-style-type: none"> All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment. |
| Must be treated without delay ¹⁸⁶ | <ul style="list-style-type: none"> Patients with significant cirrhosis or fibrosis, including decompensated cirrhosis.¹⁸⁷ Patients exhibiting clinically significant extrahepatic manifestations, for example symptomatic vasculitis (inflammation of the blood vessels) resulting from HCV-related mixed cryoglobulinaemia (insoluble clumps of cryoglobulins in the blood), HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma. Patients with HCV recurrence after liver transplantation Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals) |
| Treatment is not recommended | <ul style="list-style-type: none"> Patients with limited life expectancy due to non-liver-related comorbidities. |

Table 4.2: EASL's recommendations on treatment of Hepatitis C

183 Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006; 55: 1350–1359 at p. 1354.

184 EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001> at p. 3.

185 Falade-Nwulia O, Sulkowski M. The HCV care continuum does not end with cure: a call to arms for the prevention of reinfection. In press (2016). DOI: <http://dx.doi.org/10.1016/j.jhep.2016.10.027>

186 EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001> at p. 5.

187 Persons with decompensated cirrhosis are at risk of dying from life-threatening complications of liver disease, and may exhibit any of the following symptoms: bleeding varices (internal bleeding), ascites (fluid in the belly), encephalopathy (confusion), and jaundice (yellowing of eyes and skin). What is decompensated cirrhosis? U.S. Department of Veterans Affairs [Internet]. [cited 2016 Nov 10]. Available from: <http://www.hepatitis.va.gov/patient/complications/cirrhosis/decompensated.asp>

EASL also strongly recommends that patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection.¹⁸⁸

Anecdotes from patients interviewed in the preparation of this report indicate that persons who are still actively injecting drugs are still excluded from receiving treatment in some public hospitals, while in others priority is given to individuals who are abstinent. Several recent studies indicate that reinfection incidence is low.¹⁸⁹

HIV and HCV co-infection

HIV and HCV co-infection remains a significant issue due to the fact that co-infected patients have higher risk of fibrosis progression as compared to mono-infected patients.¹⁹⁰ Treatment is also associated with an increased risk of hepatotoxicity,¹⁹¹ although incidence is reduced in treatment with DAAs as compared to pegylated interferon-ribavirin.

Drug-drug interactions must be carefully considered in the setting of co-infection with HIV.¹⁹² For example, the pan-genotypic regimen sofosbuvir/velpatasvir¹⁹³ cannot be co-administered with HIV drugs efavirenz, etravirine, and nevirapine,¹⁹⁴ and with daclatasvir, the dosages of the aforementioned HIV drugs would require adjustment.¹⁹⁵

In a study among 45 HIV and HCV co-infected patients in Sungai Buloh Hospital in Malaysia (predominantly genotype 3), all patients underwent 48-weeks of treatment with pegylated interferon-ribavirin, and the overall SVR was 63.6%.¹⁹⁶ 41 patients reported at least one adverse effect, with the most frequent being fatigue, and 14 reported depressive symptoms or irritability.¹⁹⁷ The authors also reported low SVR rates (20%) for cirrhotic patients. This can be contrasted with DAA combinations, with SVR rates of more than 90% with just 12 weeks of treatment among HIV/HCV co-infected patients.

There are more studies that have been conducted among co-infected Genotype 1 patients, which found 92% SVR among cirrhotic HIV/HCV patients when treated with sofosbuvir-daclatasvir (predominantly Genotype 1).¹⁹⁸

Why DAAs?

They are quite simply, better. They have higher cure rates, with shorter duration of treatment, and there are significantly less side effects. For Genotype 3, which is predominant in Malaysia and is previously considered “harder to cure” with DAAs, recent studies show that SVR at 12 weeks was 95% when treated with sofosbuvir-velpatasvir as compared to 80% when treated with sofosbuvir-ribavirin.¹⁹⁹

Who is currently receiving DAAs in Malaysia?

DAAs are being provided to very few patients in private and some public facilities, but there has been no documentation as to the actual number of patients that are being treated. Relevant for the purposes of our report (access to affordable DAAs), is the Drugs for Neglected Diseases initiative (DNDi) clinical trial testing the pan-genotypicity of sofosbuvir-ravidasvir in Malaysia and Thailand. Jean-Michel Piedagnel, the Head of DNDi South-East Asia Liaison Office, provides an explanation below:

- 188 EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001> at p. 32.
- 189 Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. *Clinical Infectious Diseases* 2013; 57 (suppl 2): S1005-S110; Aspinall EJ, Corson S, Doyle JS et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clinical Infectious Diseases* (2013) 57 (suppl 2): S80-S89; Pineda JA, Núñez-Torres R, Téllez F et al. Hepatitis C virus reinfection after sustained virological response in HIV-infected patients with chronic hepatitis C. *Journal of Infection* 2015 Nov; 71(5): 571-577.
- 190 Sulkowski MS, Benhamou Y. Therapeutic issues in HIV/HCV-coinfected patients. *Journal of Viral Hepatitis* 2007 Jun 1; 14(6): 371-386.
- 191 Sulkowski MS, Benhamou Y. Therapeutic issues in HIV/HCV-coinfected patients. *Journal of Viral Hepatitis* 2007 Jun 1; 14(6): 371-386.
- 192 EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology* (2016). <http://dx.doi.org/10.1016/j.jhep.2016.09.001> at p. 10.
- 193 Velpatasvir is estimated to receive regulatory approval in Malaysia in 2017.
- 194 EASL, supra at 7.
- 195 Ibid.
- 196 Tan SS, Leong CL, Lee CKC. Treating hepatitis C in HIV/HCV co-infected patients in Malaysia: the outcomes and challenges. *Medical Journal of Malaysia* 2015 Oct; 70(5): 281-287 at p. 284.
- 197 Tan SS, Leong CL, Lee CKC. Treating hepatitis C in HIV/HCV co-infected patients in Malaysia: the outcomes and challenges. *Medical Journal of Malaysia* 2015 Oct; 70(5): 281-287 at p. 284.
- 198 Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A et al. Daclatasvir plus sofosbuvir for HCV in patients coinfecting with HIV-1. *The New England Journal of Medicine* 2015 Aug 20; 373: 714-725.
- 199 Foster GR, Afdhal N, Roberts SK, Br u N et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *New England Journal of Medicine* 2015; 373: 2608-2617.

Hepatitis C

DNDi HCV project: Enabling a public health approach for HCV patients in LMICs

Jean-Michel Piedagnel
 Head of DNDi South-East Asia Regional Office
 Drugs for Neglected Diseases initiative

The cornerstone of a public health approach to HCV is the availability of affordable and easy-to-use treatment tools that will, to the greatest extent possible, enable the same regimen(s) to be used for all HCV patients, regardless of genotype, liver disease stage, HIV co-infection, or source of infection.

Accessing compounds in late-stage development through licensing, was an early component of the DNDi strategy for HCV, to save time and resources and rapidly proceed to clinical studies for registration in countries willing to join the DNDi initiative.

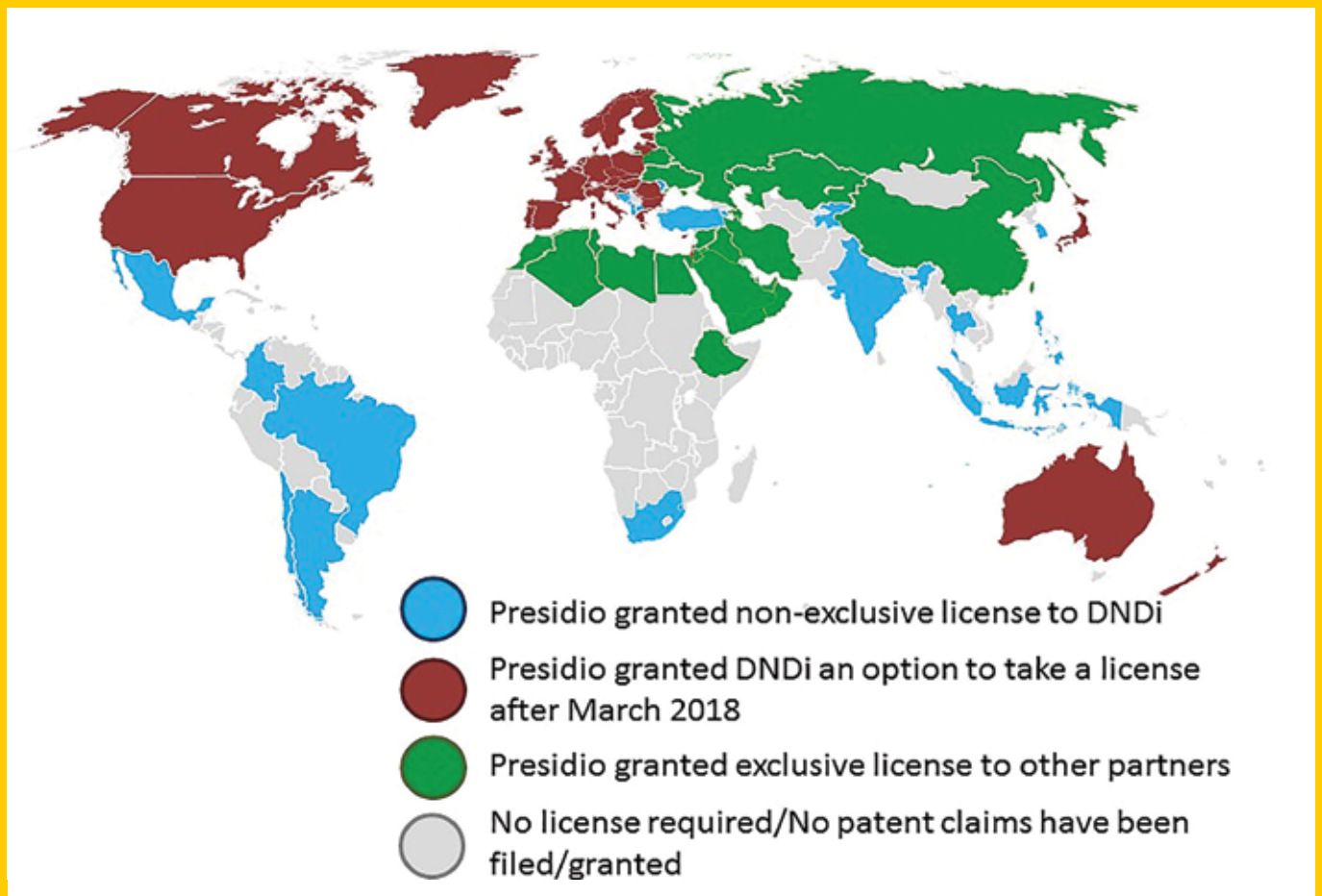
Sofosbuvir produced by Pharco (Egyptian Company) and Ravidasvir licensed to DNDi by Presidio (California Biotech) has been chosen for the Public Health demonstration. Sofosbuvir is the back bone of most HCV treatments. Evidence on Ravidasvir plus Sofosbuvir efficacy for HCV Genotype 4 was very convincing for DNDi to negotiate a very innovative licence agreement with Presidio.

Most middle income countries excluded from the Gilead and BMS licences are now covered by the non-exclusive Ravidasvir licence to DNDi.

A public health approach for resource-limited settings will be taken, including simplified models of care that allow for decentralization to the primary healthcare level, task shifting of clinical and non-clinical services, and reduced dependence on genotyping and other sophisticated laboratory monitoring.

The DNDi is proposing a two-step project with a focus on:

1. **Regional research & development (R&D):** In the medium term, DNDi and the Thai and Malaysian MOH will conduct Phase III clinical trials in Malaysia, Thailand, and other countries notably in Vietnam and South Africa to test the efficacy of a combination of sofosbuvir (SOF, already registered for HCV) + ravidasvir (RDV, a promising drug companion for sofosbuvir) as a pan-genotypic treatment towards a public health approach for tackling the HCV epidemic.
2. **Support affordable access:** A global advocacy strategy will encourage and support countries such as Vietnam and Myanmar to develop alternative treatments with favourable licensing/access terms, patent oppositions, compulsory licensing, and voluntary licensing.



The Clinical Trial in Malaysia

Genotype 3, the main HCV genotype in Malaysia, is not well studied in clinical trials with DAAs. The objective of the clinical trial in Malaysia is to enable a public health approach using Direct Acting Antivirals. The trial is co-sponsored by DNDi and the Malaysian MOH and collaborates with CRM and CRC.

This project includes conducting clinical trials to prove SOF and RAV in combination can be a public health tool for use across genotypes in Malaysia. This project also may include conducting phase 2 and/or additional phase 3 trials for in-licensed compounds that could potentially result in a new DAA-based regimen for pan-genotypic use.

The identified sites are:

| No. | Center | State | Investigators |
|-----|----------------------------------|--------------------|---|
| 1 | University Malaya Medical Center | Kuala Lumpur | Assoc.Prof Dr Chan Wah Kheong Prof Dato Dr Goh Khean Lee Prof Dr Adeeba Kamarulzaman Dr Sharifah Faridah Syed Omar |
| 2 | Hospital Selayang | Selangor | Dr Haniza Omar Dr Tan Soek Siam* Dr Hamiza Shahar Dr Syuhada Dan Binti Adnan Dr Chung Yun Chien Dr Lim Chee Sang Dr Ooi Boon Han |
| 3 | Hospital Ampang | Selangor | Dr Hajjah Rosaida Hj Mohd Said Dr Sattian Kollanthavelu Dr Ahmad Najib Azmi |
| 4 | Hospital Sultanah Bahiyah | Kedah (Alor Setar) | Datuk Dr Muhammad Radzi Abu Hassan Dr Muhammad Firdaus Bin MD. Salleh Dr Shafarul Halimi Bin Mohamed Dr Kiew Kuang Kiat Dr Zalwani Zainuddin Dr Chiam Keng Hoong |
| 5 | Hospital Sungai Buloh | Selangor | Dr Suresh Kumar Dr Ng Tiang Koi |
| 6 | Hospital Tengku Ampuan Afzan | Pahang (Kuantan) | Dr Tee Hoi Poh Dr Azlida Che Aun Assoc Prof Dr Mohd Hadzri Hasmoni |

* Dr Tan Soek Siam (highlighted in yellow) is the National Principal Investigator.

As of 14 November 2016, 231 patients have been screened and 149 patients have been included in the clinical trial in Malaysia out of 220 for the first phase of the trial. It is expected to include another 200 patients in the phase 2 of the trial.

Conclusion

In the midst of worldwide and domestic excitement on the efficacy of DAAs, the reality is that pegylated interferon-ribavirin will remain the “standard of care” for HCV-infected patients. With the results of the DNDi trial within the next few years, exciting closed-door negotiations underway, and external pressure resulting from the WHO viral hepatitis targets, it is only a matter of time before DAAs are offered to all patients living with HCV who are eligible for treatment.

Chapter 5:

Intellectual property and HCV: Barriers & Solutions

Fifa Rahman and Chee Yoke Ling

Due to external trade pressures on intellectual property, shrinking health budgets, and internal civil society pressure citing the fundamental right to health, governments find themselves in a precarious policy space.²⁰⁰ This chapter seeks to articulate how intellectual property affects access to HCV generics, the use of compulsory licenses in accordance with international law, and presents some evidence on concerns relating to such use.

Disebabkan oleh tekanan dagangan luar terhadap harta intelek, belanjawan kesihatan yang berkurangan dan tekanan dalaman daripada masyarakat sivil yang memperjuangkan hak-hak kesihatan, kerajaan kini berada dalam ruang penggubalan dasar yang sempit. Bab ini mengupas bagaimana harta intelek menjejaskan akses kepada ubat-ubatan generik hepatitis C, penggunaan lesen wajib menurut undang-undang antarabangsa, dan mengutarakan bukti berkenaan dengan kebimbangan terhadap isu pengeluaran lesen wajib untuk mengimport ubat-ubatan generik tersebut.

The “originator” pharmaceutical industry earns profits by monopolising the market and the production of their medicine. These monopolies come in the form of patents, data exclusivity, market exclusivity, and other restrictions mandated either by the World Trade Organisation, or via international trade agreements. Countries that are members of the WTO must adhere to the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), which mandates a 20-year patent from the date of filing of the application, among other things. Countries that go beyond the TRIPS agreement are said to be TRIPS-plus. However, the fundamentals of patent law state that patents should only be granted if the invention is new, involves an inventive step, and has industrial applicability. There are also exclusions, exceptions and limitations to patent claims in recognition of the needs of development and public interests, including public health. These fundamentals are contained in the TRIPS agreement and commonly referred to as “flexibilities” that WTO Members are entitled to enact in their national patent law.

Why does this matter for HCV?

The new direct-acting antivirals (DAAs) are priced really arbitrarily and exorbitantly, and are granted these monopolies. Of particular concern is sofosbuvir, which is the backbone of any HCV treatment regime. As discussed in Chapter 1 of this report, pursuant to a U.S. Senate investigation, it was discovered that the price for sofosbuvir (USD \$84,000 for 12 weeks’ treatment) was decided based on maximisation of revenue,²⁰¹ not based on research and development costs. In fact, Gilead has already recouped the R&D and procurement costs of sofosbuvir. Sofosbuvir was actually developed by Pharmasset Ltd, the company which Gilead bought over primarily because of the projected profitability of sofosbuvir. While the Malaysian government has been offered the price of USD \$12,000, bioequivalent generics are available for much less i.e. USD \$200-1000, and this means that patients will not be able to access these generics until the expiry of the monopolies. Meanwhile, Gilead has signed a voluntary licence with several generic producers for the supply of affordable alternatives, but the licence excludes Malaysia and other middle-income countries.

At time of writing there have been 27 types of patents filed in regard to sofosbuvir worldwide²⁰² for example, patents on the prodrug²⁰³ processes, etc. The following table illustrates patent applications for sofosbuvir-based regimens in Malaysia:

-
- 200 Bird RC. Developing nations and the compulsory licence: maximizing access to essential medicines while minimizing investment side effects. *The Journal of Law, Medicine & Ethics* 2009; 37(2): 209-221
- 201 Wyden R, Grassley CE. The price of Sovaldi and its impact on the U.S. health care system. U.S. Senate Committee on Finance [Internet]. 2015 Dec [cited 2016 Oct 25] at p. 44. Available from: [http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20\(Full%20Report\).pdf](http://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf)
- 202 Patent situation of key products for the treatment of hepatitis C: sofosbuvir working paper. World Health Organisation (WHO) [Internet]. 2016 Jun [cited 2016 Nov 3]. Available from: http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report.pdf
- 203 A prodrug is a precursor of a drug, which undergoes a chemical conversion by metabolic processes in the body before becoming therapeutically active. Correa C. Guidelines for the examination of patent applications related to pharmaceuticals. New York: UN Development Programme (UNDP) [Internet]. 2016 Jun 9 [cited 2016 Nov 3] at p. 14. Available from: <http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applications-relating-t.html>

| Product Name | Patent Description | Patent Status | Patent Application Date (dd/mm/yyyy) | Patent Application Number | Expected Expiry Date (dd/mm/yyyy) |
|---|------------------------------|---------------|--------------------------------------|---------------------------|-----------------------------------|
| Sofosbuvir 400 mg | Sofosbuvir compounds family | Granted | 28/04/2004 | MYPI 20041584 | 28/04/2024 |
| | Sofosbuvir prodrug | Filed | 26/03/2008 | MYPI 2013700240 | 26/03/2028 |
| | Sofosbuvir prodrug | Granted | 26/03/2008 | MYPI 20094079 | 26/03/2028 |
| | Sofosbuvir processes | Filed | 20/05/2010 | MY 2011005625 | 20/05/2030 |
| | Sofosbuvir compositions | Filed | 27/11/2012 | MYPI2014001520 | 27/11/2032 |
| | Sofosbuvir compositions | Filed | 27/11/2012 | MYPI2014001520 | 27/11/2032 |
| Sofosbuvir / ledipasvir 400/90 mg | Sofosbuvir compounds family | Granted | 28/04/2004 | MYPI20041584 | 28/04/2024 |
| | Sofosbuvir prodrug | Filed | 26/03/2008 | MYPI 2013700240 | 26/03/2028 |
| | Sofosbuvir prodrug | Granted | 26/03/2008 | MYPI20094079 | 26/03/2028 |
| | Sofosbuvir processes | Filed | 20/05/2010 | MY2011005625 | 20/05/2030 |
| | Sofosbuvir compositions | Filed | 27/11/2012 | MYPI2014001520 | 27/11/2032 |
| Sofosbuvir / Velpatasvir 400/100 mg | Sofosbuvir compounds family | Granted | 28/04/2004 | MYPI20041584 | 28/04/2024 |
| | Sofosbuvir prodrug | Filed | 26/03/2008 | MYPI 2013700240 | 26/03/2028 |
| | Sofosbuvir prodrug | Granted | 26/03/2008 | MYPI20094079 | 26/03/2028 |
| | Sofosbuvir processes | Filed | 20/05/2010 | MY2011005625 | 20/05/2030 |
| | Velpatasvir compounds family | Filed | 16/11/2012 | MYPI2014001415 | 16/11/2032 |
| | Sofosbuvir compositions | Filed | 27/11/2012 | MYPI2014001520 | 27/11/2032 |

Table 5.1: Patent Status for sofosbuvir in Malaysia²⁰⁴

Based on these, the sofosbuvir monopolies will last until 2028. Other patents have been filed, and these pending applications, if granted, may extend the monopoly to 2032.²⁰⁵

Sofosbuvir needs to be combined with other drugs to treat HCV, for example, daclatasvir or ledipasvir, meaning that governments will need to budget for these combinations and not just sofosbuvir. A pan-genotypic treatment, sofosbuvir+velpatasvir, is estimated to cost around USD \$74,760²⁰⁶ (RM313,500) for 12 weeks' treatment. To avoid substantial cost burdens, governments have no choice but to weigh options from an intellectual property perspective.

In addition to, or in lieu of patents, pharmaceutical companies may apply for a term of data exclusivity, which prevents generic companies from relying on the products' test data dossiers to register generics with drug regulatory authorities, and thus prevents them from importing and/or producing generics. In Malaysia, daclatasvir, which can be used in combination with sofosbuvir to treat Genotypes 1 and 3, is not patented, but an application for data exclusivity has been filed. To date the Malaysian Pharmaceutical Regulatory Agency has not granted data exclusivity. Sofosbuvir is covered both by patents and data exclusivity. In other countries, data exclusivity has been used to block entry of generics, even in the absence of a patent. In Ukraine, for example, Egyptian company Pharco (via its distributor Europharma) first applied for marketing authorisation

of generic sofosbuvir in Ukraine on 28 November 2014. In June 2016, Gilead filed a court case against Europharma based on a 5-year data exclusivity provision contained in Ukrainian law. This is further described in Chapter 6 of this report.

Challenging weak patents

Elsewhere, there have been several patent challenges filed by international and domestic civil society on the grounds that sofosbuvir is not novel and does not satisfy the inventive step standard for patentability. While each government has the right to determine how patentability requirements are defined, it is generally accepted that when making a decision on whether an inventive step was involved in the creation of the final product, the judgment must be made by a person skilled in the art, with ordinary knowledge or expertise in the field.²⁰⁷ This requirement is intended to confine the granting of patents to inventions that go beyond 'normal product design and development',²⁰⁸ rather than granting them to minor or trivial developments that block further innovation.²⁰⁹ Sofosbuvir was developed by Pharmasset Ltd, which filed the first patent in 2003.²¹⁰ The contention is that Gilead's patents are insufficiently inventive because the finished product was simply part and parcel of normal design and development. Indeed, the World Intellectual Property Organisation (WIPO) in its International Search Report has stated that not all sofosbuvir patent claims meet both the novelty and inventive step requirements.²¹¹

204 MedsPaL: the medicines patents and licences database. Medicines Patent Pool [Internet]. [cited 2017 May 3]. Available from: <http://www.medsdal.org>
 205 Ibid.
 206 Sofosbuvir-Velpatasvir (Epclusa). Hepatitis C Online [Internet]. [cited 2016 Nov 4]. Available from: <http://www.hepatitisc.uw.edu/page/treatment/drugs/epclusa>
 207 Correa C. Guidelines for the examination of patent applications related to pharmaceuticals. New York: UN Development Programme (UNDP) [Internet]. 2016 Jun 9 [cited 2016 Nov 3] at p. 14. Available from: <http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applicationsrelating-t.html>
 208 Barton JH. Non-obviousness. IDEA 2003; 43(3): 475-508
 209 Correa C. Guidelines for the examination of patent applications related to pharmaceuticals. New York: UN Development Programme (UNDP) [Internet]. 2016 Jun 9 [cited 2016 Nov 3] at p. 14. Available from: <http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applicationsrelating-t.html>
 210 Patent situation of key products for the treatment of hepatitis C: sofosbuvir working paper. World Health Organisation (WHO) [Internet]. 2016 Jun [cited 2016 Nov 3]. Available from: http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report.pdf
 211 Patent situation of key products for the treatment of hepatitis C: sofosbuvir working paper. World Health Organization (WHO) [Internet]. 2016 Jun [cited 2016 Nov 3]. Available from: http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report.pdf

In the sofosbuvir patent challenge at the European Patent Office (EPO), Médecins du Monde (Doctors of the World) relied on²¹² a 2007 PhD thesis²¹³ by Plinio Perrone to prove that sofosbuvir was insufficiently inventive. In an October 2016 judgment, the EPO did not accept some of Gilead's arguments on the patent and amended it.²¹⁴ The Initiative for Medicines, Access, & Knowledge, a U.S.-based non-profit working on access to medicines and intellectual property stated that as a result of this decision, generic sofosbuvir would become available in Europe in 2024 instead of 2028, but Gilead has disputed this.²¹⁵ The sofosbuvir patent was also opposed in India via a pre-grant opposition²¹⁶ procedure in 2014.

On these points, the UNDP has recommended that national patent offices and national laws use the flexibilities allowed by the TRIPS Agreement with regard to the concept of invention and in defining patentability standards.²¹⁷ It is noteworthy that in Egypt, Gilead's sofosbuvir patent application was rejected, and consequently since September 2015 government health facilities have been using six locally produced generics of sofosbuvir priced at US\$ 87 per bottle for a month's use.

Malaysia's Patents Act 1983 (last amended in 2006) requires novelty, inventive step and industrial applicability, and the Guidelines for Patent Examination (October 2011) of the Malaysian Intellectual Property Corporation (MyIPO) are used to determine patentability. Domestic generic manufacturers, health and consumer organizations and patient communities are concerned that the Guidelines and practice of MyIPO allow for weak patents to be granted. This means that the novelty and inventive step criteria are lax and need to be reviewed, particularly for public health objectives.

Malaysian law provides for post-grant invalidation of a patent, and not pre-grant challenges. Even then, patent challenges have to be filed at the High Court, which is burdensome in terms of cost and procedures. The TRIPS Agreement requires administrative procedures and this is what most countries have done. In India the existence of pre-grant opposition has resulted in preventing some life-saving medicines from being patented.

Myths and fears around compulsory licensing

The use of compulsory licenses, or even the threat of their use, often results in a 'full-fledged temper tantrum'²¹⁸ by the global pharmaceutical industry, who according to Ho (2011), 'analogue legal exceptions to patent rights (such as compulsory licensing) to stealing.'²¹⁹ Defunding of production facilities and threats to be put on the U.S. Special 301 watch list (described below) has been attributed to the issuance of these licences and the tantrums resulting therefrom.²²⁰ Hence, despite compulsory licenses being a fully legal public health tool, governments are often reluctant to issue them. Below, we examine the facts.

Myth 1

Compulsory licenses do not necessarily result in lower medicine prices.

Fact

Compulsory licenses have allowed millions of patients in both developing and developed countries access cheaper medicines.

In 2015, Beall et al. claimed that compulsory license prices exceeded median international procurement prices in 19 out of 35 case studies that they conducted.²²¹ Noted economist and former Director of the WHO Secretariat on Public Health, Innovation and Intellectual Property, German Velásquez, and former Executive Director of the MSF Access Campaign, Tido von Schoen-Angerer, denounced this study as having a flawed methodology, stating that not only did the authors present the two options as if they were equally available and alternative procurement options, but they also did not consider the patent status of the antiretrovirals to compare prices.²²² Given that compulsory licenses are used to override the patent of a medicine that is exorbitantly priced, the correct approach would be to compare price reductions from CL to the price of the existing patented drug available in the market.²²³ 't Hoen and Bermudez (2015) also criticised the article, stating that it was based on a 'lack of understanding of the international medicines market'.²²⁴

- 212 Grounds for the decision (annex) – opposition. European Patent Office [Internet] 2016 Oct 31 [cited 2016 Nov 3]. Available from: <https://register.epo.org/application?number=EP08732818&lng=en&tab=doclist>
- 213 Perrone P. Design, synthesis and biological evaluation of novel nucleotide prodrugs as potential anti hepatitis C virus agents [PhD thesis]. [Cardiff (UK)]: Cardiff University; 2007. [cited 2016 Nov 4] Available from: <http://orca.cf.ac.uk/54327/>
- 214 Grounds for the decision (annex) – opposition. European Patent Office [Internet] 2016 Oct 31 [cited 2016 Nov 3]. Available from: <https://register.epo.org/application?number=EP08732818&lng=en&tab=doclist>
- 215 Silverman E. European regulator amends some Gilead hep C patent claims. STAT [Internet]. 2016 Oct 5 [cited 2016 Nov 3]. Available from: <https://www.statnews.com/pharmalot/2016/10/05/gilead-sovalid-europe-invalidated/>
- 216 Initiative For Medicines, Access & Knowledge (I Mak) and Delhi Network Of Positive People (Dnp+) Opposition, Sofosbuvir (Gs7977), (6087/Delnp/2005). Patent Opposition Database [Internet]. 2014 Mar 17 [cited 2016 Nov 3]. Available from: https://www.patentoppositions.org/en/drugs/sofosbuvir/patent_oppositions/53ff1d584cdb5c000200000c
- 217 Correa C. Guidelines for the examination of patent applications related to pharmaceuticals. New York: UN Development Programme (UNDP) [Internet]. 2016 Jun 9 [cited 2016 Nov 3] at p. 20. Available from: <http://www.undp.org/content/undp/en/home/librarypage/hiv-aids/guidelines-for-the-examination-of-patent-applicationsrelating-t.html>
- 218 Mullenbach E. The influence of disease on the evolution of U.S. patent law and policy towards foreign patent laws in the late twentieth to early twenty-first century. *Tulane Journal of Technology and Intellectual Property* 2005; 7: 227-248, p. 236.
- 219 Ho CM. Access to medicine in the global economy: international agreements on patents and related rights. New York: Oxford University Press, Inc; 2011. 163 p.
- 220 Mullenbach E. The influence of disease on the evolution of U.S. patent law and policy towards foreign patent laws in the late twentieth to early twenty-first century. *Tulane Journal of Technology and Intellectual Property* 2005; 7: 227-248, p. 236.
- 221 Beall RF, Kuhn R, Attaran A. Compulsory licensing did not produce lower prices for antiretrovirals compared to international procurement. *Health Affairs* 2015 Mar; 34(3): 493-501.
- 222 Velásquez G, von Schoen-Angerer T. Unfair attack to developing countries' efforts to use compulsory licenses [Internet]. 2015 Mar 6 [cited 2016 Nov 7]. Available from: http://lists.keionline.org/pipermail/ip-health_lists.keionline.org/2015-March/004915.html
- 223 Ibid.
- 224 't Hoen E, Bermudez J. Compulsory licenses for medicines. *Health Affairs* 2015 Jun; 34(6): 1068.

In 2003, in a move deemed ‘historic’,²²⁵ Malaysia issued a “government use” licence to ensure that Malaysians had access to lifesaving generic HIV drugs. This is a form of compulsory licence to import or manufacture generics for “public non-commercial use” by the government, a crucial flexibility contained in the TRIPS Agreement and in Malaysia’s Patents Act section 84 on Rights of Government.

As a result of this licence and the subsequent importation of generic Zidovudine, Didanosine, and Lamivudine/Zidovudine, the average cost of treatment per month per patient dropped from USD \$315 to USD \$58 (a 81% reduction), and government treatment capacity increased from 1,500 to 4,000 patients.²²⁶ Similar government use licences in Indonesia and Thailand have also led to cheap generics reaching large numbers of patients.²²⁷

Below are some examples of issuance of compulsory licences and government use licences to ensure access to affordable medicines, issued between 2002 and 2012 from both developing and developed countries:²²⁸

| Country | Type of Compulsory License (CL) | Reason |
|---------------|---|---|
| Malaysia | CL to local company to import for use in public hospitals | Government use |
| Mozambique | CL to Pharco Mocambique Lda for local manufacture | Condition of national emergency and extreme urgency |
| Zambia | CL to Pharco Ltd for local manufacture | Condition of national emergency and extreme urgency |
| Indonesia | Licence for Ministry of Health to appoint a pharmaceutical company for local manufacture License for Ministry of Health to appoint pharmaceutical companies for local manufacture | Government use |
| Zimbabwe | CL to Varichem to exploit patent | Emergency |
| Thailand | CL to Government Pharmaceutical Organization to manufacture efavirenz | Government use |
| Ghana | CL to import generic ARVs | Government use |
| Brazil | CL to manufacture efavirenz | Government use |
| United States | CL to Swiss company to research, manufacture and sell in the US products using Immunex tumour necrosis factor patent (exports also permitted); CL on intellectual property surrounding the RX delivery system for Drug-Eluting Stents | To correct anti-competitive practices |
| Italy | CL to manufacture active ingredients: imipenem cilastatina used in antibiotics; sumatriptan succinate used in the production of migraine medicines; finasteride used in products to treat hypertrophy of the prostate, cancer of the prostate and male-pattern baldness | To correct anti-competitive practices |
| Ecuador | License for Institute Intellectual Property to appoint a pharmaceutical company for local manufacture | For affordable ARVs |
| India | License by Controller General of Patents, Design and Trademark to a local pharmaceutical company for local manufacture | Generic manufacturer application |

Table 5.2: Some examples of compulsory licences worldwide²²⁹

225 Meland M. Malaysia issues world’s first compulsory licence. Law360 [Internet]. 2004 Feb 26 [cited 2016 Nov 7]. Available from: <http://www.law360.com/articles/1035/malaysia-issues-world-s-first-compulsory-licence>

226 Chee YL. Malaysia’s experience in increasing access to antiretroviral drugs: exercising the ‘government use’ option. Third World Network [Internet]. 2006 [cited 2016 Nov 7] at p. 14. Available from: <http://www.twn.my/title2/IPR/pdf/ipr09.pdf>

227 Khor M. Compulsory License

228 The United States itself uses this compulsory licences for a range of technologies and products: see KEI Research Note: Recent United States Compulsory Licenses (7 March 2014). http://keionline.org/sites/default/files/Annex_A_US_Compulsory_Licenses_7Mar2014_8_5x11.pdf

229 Khor M. Compulsory License and “government use” to promote access to medicines: some examples. Third World Network. 2014, p.24

Myth 2

Compulsory licenses reduce foreign direct investment (FDI) into a country, because corporations view the country as having insufficient intellectual property coverage.

Fact

There is no conclusive evidence that the issuance of a compulsory licence reduces FDI.

The issuance of a compulsory licence has been described as a challenge that can result in unwanted side effects to the levels of foreign direct investment.²³⁰ Firstly, let us look at the evidence in terms of Malaysian FDI overall with the date of issuance of the compulsory licence for HIV drugs in 2004. From the graph below, FDI to Malaysia actually increased.

FDI (USD\$ bil)

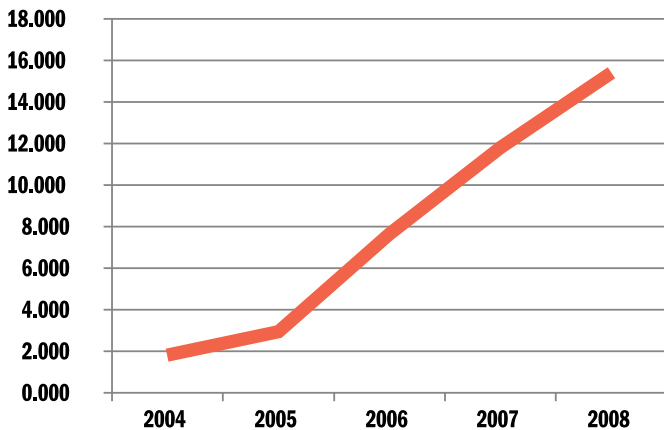


Figure 5.1: Foreign Direct Investment in Malaysia after issuance of the Compulsory Licence²³¹

The case of Thailand which issued seven government use compulsory licences between 2006 and 2008 is even more telling, with licences issued for efavirenz (for HIV, in November 2006), the lopinavir/ritonavir combination (for HIV, January 2007), clopidogrel (for the treatment of coronary artery disease, in January 2007) and four anti-cancer drugs (imatinib,²³² erlotinib, letrozole, and docetaxel, in January 2008).

In the period both prior to and following the issuance of these compulsory licenses, the impact of these actions was subject to debate. Critics, for example, warned that the US would punish Thailand harshly, and that the targeted industries would face severe losses. A report by Thailand’s Ministry of Public Health’s Health Intervention and Technology Assessment Program²³³

represents a cost-benefit analysis of the compulsory licences, with three dimensions emphasized: the health impact, the broader economic impact (notably on trade/investment), and the context of stakeholder perceptions.

At time of the compulsory licences issuance, the US accounted for 15% of Thai exports, making it Thailand’s largest export partner. Much was made of the fact that after the first three compulsory licences were issued, the US withdrew Generalised System of Preferences (GSP) status from three products, namely gold jewellery, polyethylene terephthalate in primary forms, and flat screen color televisions. (GSP status allows the exporting good to enter the US tax-free).

The report noted that there was no definitive proof of the link between the government’s issuance of the licences and the US government’s withdrawal of GSP status; furthermore, it is noted that the export levels of the industries in question already exceeded the maximum amount allowed by the US under GSP status. Nevertheless, due in large part to the perception that the two actions were linked, the report examined the impact of the loss of GSP status on the industries potentially affected, and noted that two of the three products saw net **increases** in exports of the products in question, while the overall exports of one declined only slightly.

The Thai government issued four compulsory licences (January 2008) **after** GSP on 3 products was withdrawn (July 2007), but no action was taken on the additional categories that were afforded GSP status. Furthermore, Thailand issued those four licences *after* being moved to the US Trade Representative’s Special 301 Report Priority Watch List (April 2007), with no exacerbation of the 301 Report’s classification of Thailand. Finally, as the report highlights: “A noteworthy point is that although the GSP privilege was withdrawn for the three export products in 2007, **an additional eight products were granted the GSP status in the same year, a fact which has received little attention.**”

Myth 3

If we issue a compulsory licence, the U.S. government will put us in the Special 301 priority watch list.

Fact

The issuance of a compulsory licence, along with other TRIPS flexibilities, has been acknowledged by the U.S. government to be a right of Nation States to exercise.

The Special 301 legislation requires the USTR to identify, on an annual basis and within a 30-day window, countries that ‘deny adequate and effective protection of intellectual property rights’, or that ‘deny fair and equitable market access to United States persons that rely upon intellectual property protection’.²³⁴ These countries are placed on the Special 301 watch list. The Pharmaceutical Research and Manufacturers

230 Bird RC. Developing nations and the compulsory licence: maximizing access to essential medicines while minimizing investment side effects. *The Journal of Law, Medicine & Ethics* 2009; 37(2): 209-221, p. 210.

231 Malaysia – foreign direct investment. Index Mundi [Internet]. [cited 2016 Nov 7]. Available from: <http://www.indexmundi.com/facts/malaysia/foreign-direct-investment>

232 The government use action on imatinib was suspended and never implemented, as Novartis agreed to provide the drug free under a patient assistance program.

233 Ministry of Public Health (Thailand). Assessing the Implications of Thailand’s Government Use Licenses, Issued in 2006-2008. Report by Health Intervention and Technology Assessment Program. 2009: <http://www.hitap.net/en/research/17635> The discussion in this chapter is extracted from an overview paper of the Thai report: Shashikant.S. Thailand’s Compulsory Licences Experience. Third World Network 2016 (unpublished).

234 Trade Act: Identification of Countries that Deny Adequate Protection, or Market Access, for Intellectual Property Rights 19 USC §2242(a) (1974)

of America (PhRMA) regularly input²³⁵ into the Special 301 process, and U.S. foreign policy on IP is largely consistent with their demands. The Special 301 has been stated by some to be an effective measure of external pressure on U.S. trading partners to adopt maximalist IP in national laws, including by increasing the leverage of U.S. negotiators.²³⁶ Shadlen et al. (2005) discuss the efficacy of Special 301 and state that for some it may be seen as aggressive unilateralism, and that others may only consider them 'idle threats with uncertain consequences'.²³⁷

In Malaysia, the threat of being placed on this list seems to dominate discussions on compulsory licenses, despite the measure being legal under international law. In addition, via an August 2016 letter to U.S. non-profit Knowledge Ecology International (KEI), the U.S. Department of State affirmed the rights of WTO member states to use TRIPS flexibilities, including compulsory licences. The letter is annexed to this report.

In addition, as can be seen in the case of Thailand discussed above, the country's issuance of compulsory licences for government use did not worsen their Special 301 situation.

Conclusion and Recommendations

International targets geared towards HCV elimination (WHO 2020 and 2030 viral hepatitis targets), an increasing HCV disease burden, and the fact that Malaysia at present does not diagnose or treat enough, means that intellectual property barriers must be examined and overcome. The following recommendations are made to ensure timely and sustained access to affordable medicines:

1. Review and increase the strictness of patentability standards and quality of patent application examination to prevent weak patents and the evergreening of patents;
2. Provide for pre-grant patent opposition in the Patents Act, with appropriate administrative mechanisms;
3. Put in place administrative mechanisms for patent invalidation (instead of the High Court at the first instance);
4. Reject TRIPS-plus provisions in trade agreements, including the Regional Comprehensive Economic Partnership (RCEP) under negotiations;
5. Refrain from implementing TRIPS-plus provisions in the Trans Pacific Partnership Agreement (TPPA) which will not enter into force under the current US government;
6. Exercise Malaysia's right under international law to issue compulsory licences for sofosbuvir and other drugs that are beyond the Malaysian government's pecuniary reach.

235 PhRMA. Special 301 submission 2014. (2014) <<http://www.phrma.org/sites/default/files/pdf/2014-special-301-submission.pdf>> Accessed 31 December 2015 at 4

236 Bello JH, Holmer AF. 'Special 301': its requirements, implementation, and significance. *Fordham International Law Journal* 1989; 13(3): 259-275 at 274

237 Shadlen KC, Schrank A, Kurtz MJ. The political economy of intellectual property protection: the case of software. *International Studies Quarterly* 2005; 49(1): 45-71

Chapter 6

International Case Studies: a Snapshot of the Middle-Income Country Response

Fifa Rahman, Marcela Vieira, Sergey Kondratyuk

“The big question is what will the company charge in countries they classify as ‘middle-income’ that are almost all going to be excluded from Gilead’s voluntary licensing strategy, and where the heaviest burden of the disease lies, but 75% of the world’s poor live?”²³⁸

~ Rohit Malpani, Director of Policy and Analysis
Médecins Sans Frontières (MSF)/
Doctors Without Borders Access Campaign.

“Persoalan yang besar – berapakah harga yang akan ditetapkan oleh Gilead di negara-negara yang dikategorikan sebagai ‘pendapatan pertengahan’ yang hampir kesemuanya terkecuali daripada strategi perlesenan sukarela syarikat tersebut, malah di mana beban penyakit adalah yang paling berat dan didiami 75% penduduk miskin dunia?”

~ Rohit Malpani, Pengarah Dasar dan Analisa
Doktor Tanpa Sempadan (MSF)/
Kempen Akses Doktor Tanpa Sempadan.

Introduction

The World Bank classifications of countries put middle-income and upper middle-income countries in a unique, and arbitrary, access to medicines conundrum. As a result of this categorisation, HCV high burden countries like Malaysia, China, Brazil, Thailand, and Ukraine, are left out of voluntary licences that could allow generic competition for the new direct-acting antivirals (DAAs), as well as other so-called access policies such as tier-pricing. Where countries like Egypt (included in the Gilead voluntary licence for sofosbuvir) can access the drug for USD \$900 per 12 weeks treatment,²³⁹ countries excluded from this licence must purchase drugs at innovator prices. Malaysia has been offered sofosbuvir for USD \$12,000 for 12 weeks treatment.

This situation leaves Ministries of Health and Drug Regulatory Agencies in a fix, on one hand considering the need to cure, and on the other hand, fearing international repercussions from exercising TRIPS flexibilities and issuing a compulsory licence.²⁴⁰ These international repercussions, include, for example, being placed in the U.S. government’s Special 301 Watch List²⁴¹ – which is basically the U.S. government’s ‘naughty list’ for countries that it deems does not fulfil intellectual property standards. Recently, however, in a letter dated 5 August 2016 to U.S. non-profit organisation Knowledge Ecology International, the U.S. Department of State affirmed the rights of countries

to use TRIPS flexibilities to promote access to medicines. The letter is annexed to this report. In September 2016, the UN High Level Panel on Access to Medicines emphasised that governments should retain the freedom to determine the grounds under which compulsory licences are granted, and that national laws should facilitate the prompt and expedient use of compulsory licences or government use licences,²⁴² as well as exercise fully all other public health flexibilities, such as to adopt strict examination of pharmaceutical patent applications and apply rigorous public-health sensitive standards of patentability (p. 28).

This chapter describes responses in two middle-income countries, Brazil, and Ukraine, and discusses how these are relevant to Malaysia.

Brazil

Brazil is categorised as an upper middle income country by the World Bank,²⁴³ and has an average household net adjusted disposable income of USD \$957.25 per month (MYR4012.28).²⁴⁴ From a study involving a stratified sample of 19,503 inhabitants aged between 10 and 69 years, living in all 26 State capitals and the Federal District, it was determined that HCV prevalence was 1.38%, i.e. 1.3 million individuals are living with HCV.²⁴⁵ The study also found an association between extreme poverty and risk of HCV infection.²⁴⁶

238 Malpani R. MSF responds to reports on Gilead pricing for hepatitis C drug sofosbuvir in developing countries. MSF Access Campaign [Internet]. 2014 Feb 7 [cited 2016 Oct 25]. Available from: <https://www.msfaccess.org/content/msf-responds-reports-gilead-pricing-hepatitis-c-drug-sofosbuvir-developing-countries>

239 McNeil Jr DG. Curing Hepatitis C, in an experiment the size of Egypt. The New York Times [Internet]. 2015 Dec 15 [cited 2016 Aug 30]. Available from: http://www.nytimes.com/2015/12/16/health/hepatitis-c-treatment-egypt.html?_r=0

240 A compulsory licence, or in some jurisdictions known as a ‘government use’ licence, enables countries to import generic medicines while paying a small royalty to the patent holder. It is a flexibility under TRIPS, and under the Doha Declaration, it was stated that Member states have the freedom to determine the grounds upon which such licences are granted. Declaration on TRIPS and public health. World Trade Organisation [Internet]. 2001 Nov 20 [cited 2016 Aug 30]. Available from: https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.pdf

241 2016 Special 301 Report. Office of the United States Trade Representative [Internet]. 2016 Apr [cited 2016 Aug 30]. Available from: <https://ustr.gov/sites/default/files/USTR-2016-Special-301-Report.pdf>

242 Report of the United Nations Secretary-General’s high-level panel on access to medicines: promoting innovation and access to health technologies. 2016 Sep [cited 2016 Nov 28] at p. 23. Available from: <https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/57d9c6ebf5e231b2f02cd3d4/1473890031320/UNSG+HLP+Report+FINAL+12+Sept+2016.pdf>

243 World Bank [Internet]. [cited 2016 Oct 19]. Available from: <http://data.worldbank.org/country/brazil>

244 Income, Brazil. OECD Better Life Index. [Internet]. [cited 2016 Oct 19]. Available from: <http://www.oecdbetterlifeindex.org/topics/income/>

245 Pereira LMMB, Martelli CMT, Moreira RC, Merchan-Hamman E, Stein AT et al. Prevalence and risk factors of hepatitis C virus infection in Brazil, 2005 to 2009: a cross-sectional study. BMC Infectious Diseases 2013; 13: 60-71

246 Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clinical Infectious Diseases. [Internet]. 2012 Jul 15; [cited 2016 Oct 18] 55 (suppl 1):S10-5. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/22715208>

Based on a mathematical model, Brazilian public health practitioners found that in order to control the spread of HCV, there was a need to increase the number of treatments from 15,000 per year to 45,000 treatments per year.²⁴⁷ Pursuant to this, the Department of STI, AIDS and Viral Hepatitis, among other things, conducted an evaluation of previous treatments and found low cure rates, and they proceeded to enter into intense negotiations with the manufacturers of DAAs.²⁴⁸

The current price for branded sofosbuvir in Brazil is R \$21,245 (USD \$6,000)²⁴⁹ per 12-week course. At time of writing, several rumours persist about a deal with Gilead that included a 35% price reduction for treatment in 2017, but that this has now been dropped due to rumours of the possibility of a compulsory licence being issued in Brazil. Even with this reduction, the price would be 5 times higher than Brazilian average household income, and thus is unaffordable.

In September 2016, Brazil's Minister of Foreign Relations José Serra called for concerted actions among BRICS nations on public health, including the possibility of issuing compulsory licences for HCV.²⁵⁰ Given the recent political turmoil and parliamentary coup by the conservative party, however, it is unclear whether a compulsory licence (CL) will be issued at all. In fact, Brazil has threatened to issue a CL many times in the past, including when José Serra was Minister of Health under the PSDB administration, but only one CL has actually been issued in the country, under the PT administration. It was for HIV medicine efavirenz in 2007, leading to savings in public purchases of about USD \$104 million in a five-year period.²⁵¹ It is not possible to know if a CL would actually be issued this time, especially under the current government that seems to be much more willing to take actions that favours the pharmaceutical industry and not that challenges its financial interests, as the CL is pictured. This includes accelerating the negotiations of a FTA between European Union and Mercosur, including TRIPS-plus measures and restrictions of using TRIPS flexibilities.²⁵²

Brazil has a two-step patent application procedure, with the Health Regulatory Agency (known by the Portuguese acronym ANVISA) considering it first, followed by the Patent Office (INPI). There is a huge backlog in the analysis and granting of patent applications, resulting in patent application processes that take many years. The sofosbuvir patent was filed in April 2004, and at time of writing has yet to be approved by both ANVISA and INPI. Thus, at present, there is no patent barrier

pertaining to sofosbuvir. This means that legally Brazil could both produce and import off VL-license (since Brazil is out of the geographical scope of countries authorized to buy the generics produced under the Gilead VL for sofosbuvir) generic versions of sofosbuvir. However, due to the "expectation of the right to patent protection", which could lead to the payment of damages in case the patent is granted in the future, the Brazilian MoH has decided to use the modality of purchase without bidding (exclusive to one producer, the patent applicant) in these situation.

At time of writing, there is a public-private consortium of national laboratories working on a local production of a generic version of sofosbuvir for an estimated price of USD \$3000 for 12-week treatment, with intentions to file for market approval in March 2017.²⁵³ There is also a recent joint mechanism for procurement of medicines in Mercosur countries,²⁵⁴ to which sofosbuvir is on the list of medicines that might be negotiated under this mechanism. There is the possibility of procurement from generic suppliers, including Richmond from Argentina that offered a price of USD \$1,500²⁵⁵ (MYR 6,679). These deliberations might help drive the price of sofosbuvir down in Brazil, even in the absence of a CL.

Access to medicines activism in Brazil has been largely led by non-governmental organisations working on AIDS, with the main strategy of threatening drug companies with compulsory licences and challenging unmerited patents and patents applications through oppositions.²⁵⁶ In 2001, Brazilian civil society formed the Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples (GTPI/REBRIP), which works nationally on patent examinations, price reductions, and access to generic medicines.²⁵⁷ For example, in 2005, due to exorbitant prices, the Brazilian government announced that the HIV drug Kaletra was a matter of public interest, and entered into negotiations with the drug company, Abbott, to reduce the prices. The result of this was a deal that fixed a lower price per annum for Kaletra, but prohibited the use of a compulsory licence and technology transfer for the production of the drug in Brazil.²⁵⁸

Given that international law allows for countries to issue compulsory licences, this deal was deemed as TRIPS-plus, and widely denounced by civil society and patient groups. These groups, including GTPI, began a class action suit to compel the government to issue a compulsory licence for Kaletra. The case

247 Mesquita F, Santos ME, Benzaken A, Corrêa RG et al. The Brazilian comprehensive response to hepatitis C: from strategic thinking to access to interferon-free therapy. *BMC Public Health* 2016 Nov; 16: 1132-1137.

248 Ibid 249 Brasil, Governo Federal, Portal da Transparência. [Internet]. [cited 2016 Nov 18]. Available from: <http://www3.transparencia.gov.br/jsp/contratos/contratoExtrato.jsf?consulta=3&CodigoOrgao=36000&consulta2=0&idContrato=418911>. Price per pill R\$ 252.91 (USD 71.45).

250 Remarks by minister José Serra at the BRICS foreign affairs ministers meeting on the margins of the 71st United Nations General Assembly – New York, September 20, 2016. Ministry of Foreign Affairs, Brazil [Internet]. 2016 Sep 20 [cited 2016 Oct 20]. Available from: <http://www.itamaraty.gov.br/en/press-releases/14762-intervencao-do-ministro-das-relacoes-exteriores-jose-serra-na-reuniao-de-chanceleres-dos-brics-a-margem-da-71-assembleia-geral-das-nacoes-unidas-novayork-20-de-setembro-de-2017>

251 Brazil, Ministry of Health, Compulsory licence and access to medicines: economic savings of efavirenz in Brazil, Powerpoint presented at the International Aids Conference, 2012. [cited 2016 Nov 18]. Available from: <http://pag.aids2012.org/Session.aspx?s=228>.

252 EU-Mercosur Association Agreement. Chapter on intellectual property rights [Internet]. [cited 2016 Nov 18]. Available from: http://trade.ec.europa.eu/doclib/docs/2016/november/tradoc_155070.pdf.

253 Portal Fiocruz. Fiocruz firma parceria para medicamento contra hepatite C (Fiocruz signs partnership for Hepatitis C drug) [Internet]. 2016 May 11 [cited 2016 Nov 18]. Available from: <http://portal.fiocruz.br/pt-br/content/fiocruz-firma-parceria-para-medicamento-contra-hepatite-c>.

254 MERCOSUR/RMS Ext/ACUERDO N° 05/15 - Creación del comité ad hoc para negociación de precios de medicamentos de alto costo en los estados partes y asociados del Mercosur (Creation of the ad hoc committee for the negotiation of high cost medicines in Mercosur parties and associates of Mercosur) [Internet]. [cited 2016 Nov 18]. Available from: http://www.mercosur.int/innovaportal/file/7497/1/rms_2015_acta01ex_ane03_es_acuerdo05_creacioncahpm.pdf

255 Argentina, Ministerio de la Salud. Mercosur y Estados Asociados definieron compra conjunta de un medicamento para tratar VIH. 2015 Nov 13 [cited 2016 Nov 18]. Available from: <http://www.msal.gov.ar/prensa/index.php/articulos/lista-deslide-de-destacados/2964-mercursos-y-estados-asociados-definieron-compra-conjunta-de-un-medicamento-para-tratarhepatitis-c>.

256 Chaves GC, Vieira MF, Reis R. Access to medicines and intellectual property in Brazil: reflections and strategies of civil society. *International Journal on Human Rights* 2008; 5(8): 163-189 at 170

257 Ibid at 175

had a negative decision at first instance, with the ruling of the judge explicitly mentioned that Brazil could face commercial retaliations from the U.S. for issuing a CL (even if this is not true, it was the main motivation issued by the judge to rule against the CL). GTPI appealed from this first decision and the case is still pending decision by the appeal court. Even if a CL was never issued for Kaletra in Brazil, the deal with Abbott was afterwards cancelled and the price dropped in following years, as a consequence of the CL issued in Thailand for Kaletra in 2007. Access to HCV medicines activism is being led by the same organisations.

In regard to access to HCV medicines, in 2015, GTPI filed patent oppositions against Gilead's applications for sofosbuvir,²⁵⁹ on the grounds that the drug is not new and does not involve an inventive step, which is a prerequisite for the granting of patents.²⁶⁰ In November 2016, GTPI also filed a pre-grant patent opposition related to daclatasvir, another DAAs, on the grounds that the patent application doesn't fulfill the patentability requirement of inventive step.²⁶¹ At time of writing, daclatasvir is sold in Brazil with exclusivity by Bristol-Myers Squibb (BMS) for the price of USD \$2,200 (MYR 9,795) per 12-week treatment, while studies estimate that the cost of production for the same period of treatment would be around US\$ 22.²⁶² Many civil society organizations in Brazil are also protesting against the high prices of the new DAAs, on the basis of violation of the principle of universal access to health care contained in the Brazilian Constitution given that the medicines are being offered only to those in more advanced stages of the disease.²⁶³

Ukraine

Ukraine is categorised as a lower middle-income country by the World Bank²⁶⁴, and average monthly wages are at USD \$207.64 per month (MYR 900.55).²⁶⁵ Over 5% of the general population is infected with HCV,²⁶⁶ putting absolute figures at about 2 million people. This is one of the highest HCV prevalence figures in the world. Despite this, Ukraine is excluded from the Gilead voluntary license as it is seen as a 'profit-making commercial market' for sofosbuvir.²⁶⁷ Among the PWID population (est. 310,000 people), HCV prevalence has been estimated at 55%.²⁶⁸ Among all new registered HIV cases, 36.3% are HIV/HCV co-infected.²⁶⁹ War in the east of Ukraine has been cited as a driver of the HCV epidemic owing to the deterioration of sanitary, social, and economic conditions in those areas, and the inability to provide HCV services in the combat zones.²⁷⁰

In 2015, a special price was negotiated with Gilead by an NGO (Alliance for Public Health) for the treatment of 1500 patients, including people who inject drugs and HIV/HCV co-infected patients at the price of USD \$300 per patient for a 28 day supply. The project, funded by international donors, has been deemed a success, with 379 patients, including 366 of those with HIV/HCV co-infection, having access sofosbuvir treatment from the project launch date up to 1 February 2016.²⁷¹

Ukraine, however, is undergoing some challenges in terms of intellectual property of sofosbuvir. Branded sofosbuvir was costed to the MoH Ukraine and UNDP in March 2016 at USD \$1,500 (MYR 6,679) per treatment course. Entry of the generic sofosbuvir (Grateziano) from the Egyptian generics producer Pharco into the Ukrainian market in June 2016, could have possibly decreased the price of sofosbuvir to approximately USD \$755.42 (MYR 3276.31) for a 12 weeks treatment course. Via a subsequent state-funded tender, the price for Grateziano was fixed at USD \$711 (MYR 3,166) for a 12-week treatment course.²⁷²

Sofosbuvir is not patented in Ukraine due to several pre-grant oppositions filed by the All-Ukrainian Network of PLWHA with support of IRF Ukraine/Open Society Foundations (OSF), but is currently subject to a challenge on data exclusivity. All pharmaceuticals that were filed for registration in Ukraine within two years of the first market authorisation in the world (whether this is at the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), etc) are automatically granted a 5-year period of data exclusivity with a possibility of 1 year extension for new indications.

Gilead applied for and received marketing authorisation on 9 June and 9 October 2015 respectively. On 18 November 2015, Pharco, the Egyptian producer of generic sofosbuvir, received marketing authorisation, and exported generic sofosbuvir (Grateziano) to Ukraine. In June 2016, Gilead filed a court case against Europharma International LLC (Pharco Pharmaceuticals distributor in Ukraine), the Ukrainian Drug Regulation Authority, and the Ministry of Health. Gilead claimed that their data exclusivity period was still valid, and that the registration of Grateziano by Pharco was legally void.

The Kiev Administrative Court at first instance dismissed Gilead's claims as Pharco had filed application for marketing authorization 7 months earlier than Gilead, which means that Pharco and Ukrainian drug regulatory agency had not relied on the test data submitted by Gilead to Ukrainian drug regulatory agency, thus there was no infringement of data exclusivity

258 Ibid at 178

259 GTPI [Internet]. [cited 2016 Dec 5]. Available from: http://deolhonaspentes.org/wpcontent/uploads/2016/02/GTPI_sofosbuvir_subsidio_final.pdf.

260 The grounds for opposing patents on sofosbuvir in Argentina, Brazil, China, Ukraine, and Russia. I-MAK [Internet]. 2015 May 20 [cited 2016 Oct 20]. Available from: http://static1.1.sqspcdn.com/static/f/129694/26244685/1432089253573/briefing+note_HepC_sofosbuvir_PatentOppositio ns_20+May+2015.pdf?token=bnsN6A4%2BZ2NfBZiEcDWI250r9bl%3D

261 GTPI [Internet]. [cited 2016 Dec 5]. Available from: http://deolhonaspentes.org/wpcontent/uploads/2016/11/daclatasvir_final.pdf.

262 Hill A, Simmons B, Gotham D, Fortunak J. Rapid reductions in prices for generic sofosbuvir and daclatasvir to treat hepatitis C. *Journal of Virus Eradication* 2016; 2: 28-31.

263 Among others, see: GTPI. Protesto em João Pessoa – Abertura do congresso de Aids e Hepatites. 2015 Nov [cited 2016 Nov 2016]. Available from: <http://deolhonaspentes.org/4682-2/>.

264 World Bank [Internet]. [cited 2016 Nov 15]. Available from: <http://data.worldbank.org/country/ukraine>

265 Ukraine average monthly wages. Trading Economics [Internet]. [cited 2016 Nov 11]. Available from: <http://www.tradingeconomics.com/ukraine/wages>

266 Over 5% of Ukrainians are infected with hepatitis C. Alliance for Public Health [Internet]. 2016 Feb 25 [cited 2016 Nov 15]. Available from: <http://aph.org.ua/en/news/over-5-of-ukrainians-are-infected-with-hepatitis-c/>

267 Forette C. Gilead's license on hepatitis C drugs, sofosbuvir and ledipasvir: a fool's bargain. HepCoalition [Internet]. 2014 Oct 10 [cited 2016 Nov 15]. Available from: <http://www.hepcoalition.org/advocate/advocacy-tools/article/gilead-s-license-on-hepatitis-c-drugs-sofosbuvir-and-ledipasvir-a-fool-s>

268 Filippovych S. Introduction of sofosbuvir-based HCV treatment in Ukraine. International HIV/AIDS Alliance in Ukraine [Internet]. 2015 Dec 1 [cited 2016 Nov 15]. Available from: <http://www.bhiva.org/documents/Conferences/EHHC/2015/Presentations/151210/SergiiFilippovych.pdf>

269 Ukrainian Center for Socially Dangerous Disease Control of the Ministry of Health of Ukraine, bulletin # 45 p.27. [cited 2016 Nov 16, translated by Sergey Filippovych, Alliance for Public Health]. Available from: http://ucdc.gov.ua/en/pages/diseases/hiv_aids/monitoring/information-bulletins

270 Hepatitis C: war in the east of Ukraine is a driver of the epidemic!: press release. International HIV/AIDS Alliance in Ukraine [Internet]. 2015 Jul 28 [cited 2016 Nov 15]. Available from: http://www.aidsalliance.org.ua/ru/news/pdf/01-12_2015/07/dayc_en.pdf

271 Successful results of sofosbuvir-based treatment of HepC! Alliance for Public Health [Internet]. 2016 Feb 16 [cited 2016 Nov 16]. Available from: <http://aph.org.ua/en/news/successful-results-of-sofosbuvir-based-treatment-of-hepc/>

272 Notification on Acceptance of Proposal by Institute of Epidemiology and Infectious Diseases by Gromashevskiy. State portal on Ukraine government procurements. [cited 2016 Nov 16, translated by Sergey Kondratyuk, All-Ukrainian Network of PLWH]. Available from: https://tender.me.gov.ua/EDZFrontOffice/menu/uk/purchaseStartSearch/announce_detail/announce_detail?id=EDZrrrPn9T All quoted prices are exclusively proposed for government-funded procurement.

occurring as a result of the Grateziano registration. Gilead appealed the decision and as of November 2016, the case is still pending consideration by the Kiev Appellate Administrative Court.

What this means is that if Gilead wins the case, generic sofosbuvir will be de-registered and withdrawn from the market in Ukraine, depriving millions of treatment.

In parallel to this action, Gilead launched a pre-investment dispute settlement procedure against the Ministry of Justice and MoH Ukraine. While the procedure is conducted in secret and patient groups and Europharma (the generic medicine distributor) were not allowed to participate in the hearing, leaked information indicates that Gilead has threatened to sue the Ukrainian government for USD \$5 million at the International Centre for the Settlement of Investment Disputes (ICSID) in Washington D.C., on the basis that Ukraine infringed their investment rights under a 1994 Ukraine-United States bilateral investment treaty concerning the Encouragement and Reciprocal Protection of Investment.²⁷³

In relation to other DAAs, the Gilead-proposed price for Harvoni (sofosbuvir/ledipasvir) is USD \$900 (MYR 4007.42) per treatment course, and Epclusa (sofosbuvir/velpatasvir) is expected to be priced similarly.²⁷⁴ The expected price for Vimvi (known elsewhere as Viekira Pak or Viekirax) (dasabuvir, ombitasvir, paritaprevir, and ritonavir), is USD \$3,200 (MYR 14,248.63) per treatment course.²⁷⁵

What are the Takeaways for Malaysia?

Inequities resulting from middle-income country classification

While there is no universally agreed definition of middle-income countries, the World Bank definitions are widely relied on. The World Bank definitions of middle-income incomes continue to be used arbitrarily to exclude patients from accessing essential medicines. Doctors without Borders/Médecins Sans Frontières states that it is an 'artificial classification that is not linked to public health realities on the ground',²⁷⁶ illustrating that more than half of its programmes are conducted in middle-income countries.

In addition, middle-income countries are increasingly deemed ineligible for essential health-systems strengthening funding from international funders based on the World Bank classifications.

From this, an imperative emerges for public health practitioners to begin advocacy to address the inequities resulting from middle-income categorisation. This could include the redefinition of income categorisations, or a comprehensive review on the impact of its classifications in public health delivery.

Global struggles for a balanced IP regime that prioritises access to medicines

Ever since the inclusion of intellectual property (IP) in international trade agreements, governments have lived in fear of offending multinational corporations, while at the same time knowing that inadequate provision of health services and the inability to cure will devastate whole populations. In Brazil, while there is no patent for sofosbuvir, the fear of IP repercussions means that the government decided to purchase the drugs from the 'originator' company at prices much higher than the generics.

IP is oft-quoted by corporations and governments promoting maximalist IP through trade as necessary to reward innovators and to ensure they keep innovating. These monopolies have created a system where the prices of drugs are maximised to earn profit, and corporations are producing drugs mainly for more affluent markets. As a result, public-private partnerships like DNDi have sprouted to innovate drugs for diseases that corporations have neglected simply because producing drugs for them simply because they are not profitable.

Calls are also intensifying for a reform of how pharmaceuticals are researched, developed, and linked to the price of the final product. 'Delinkage' would involve governments replacing monopoly-based incentives with cash-based incentives, research and development subsidies, and prizes, and this would progressively reduce drug prices closer to the prices of the generics.²⁷⁷ In September 2016, the UN Secretary-General's High Level Panel on Access to Medicines endorsed delinkage and called for a coordinated global R&D agenda.²⁷⁸

In addition to this, pharmaceutical regulatory bodies should take note of the impact of biased investor-state dispute settlement proceedings that can be used to decimate health budgets and prevent entry of generics.

CONCLUSION

There are key similarities on the access to medicines struggle in these middle-income countries, but the international response of these countries are fragmented. Given these similarities, and increasing attention to reform of drug pricing systems at international arena, there is a real opportunity for cross-regional joint strategies and coordination on these issues. Governments must become more invested in tackling the middle-income country struggle.

273 Treaty between the United States of America and Ukraine concerning the encouragement and reciprocal protection of investment. U.S. Department of State [Internet]. 1994 Mar 4 [cited 2016 Dec 9]. Available from: <http://www.state.gov/documents/organization/210531.pdf>

274 Personal communication, CF "Patients of Ukraine", Nov 2016

275 Personal communication, All-Ukrainian Network of PLWHA, Nov 2016.

276 As HIV burden overwhelmingly shifts to 'middle-income' countries, access to affordable medicines is under threat. Médecins Sans Frontières Access Campaign [Internet]. 2015 Jul 21 [cited 2016 Nov 29]. Available from: <http://www.msfaaccess.org/about-us/media-room/press-releases/middle-income-countries-access-threats>

277 Love J. Inside views: delinkage of R&D costs from product prices. Intellectual Property Watch [Internet]. 2016 Sep 15 [cited 2016 Nov 30]. Available from: <http://www.ip-watch.org/2016/09/15/delinkage-of-rd-costs-from-product-prices/>

278 Report of the United Nations secretary-general's high-level panel on access to medicines: promoting innovation and access to health technologies [Internet]. 2016 Sep [cited 2016 Nov 30] at p. 29-30. Available from: <https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/57d9c6ebf5e231b2f02cd3d4/1473890031320/UNSG+HLP+Report+FINAL+12+Sept+2016.pdf>

Chapter 7

Capturing the Patient Voice

Compiled by Shangeetha Thirumayni



Alice

47, mother of three children

I was first diagnosed with hepatitis C in 1991 as part of a routine blood test. When they told me I was positive, I was like “What is Hep C?” and “Why me?” I wondered how I got it, and realised that the only way I could’ve contracted it was through the platelet transfusion I had when I was warded for dengue. I went home and did more research on it, and I could tell that the doctors didn’t really know how to treat it. I then began treatment with pegylated interferon-ribavirin, and throughout the years relapsed five times. It was at that time when I felt so helpless. But after a few relapses, you go: life goes on, you know? I planned my marriage, and conceiving children between my treatments.

Then the DAAs came out, but they weren’t available here. In 2015, I went overseas to get treated and it was very expensive, but now I am cured. I have faith that I have recovered, that I am healed. It’s a real lifesaver. But I’m thinking, I can afford this treatment, but there are many others who can’t. I have a friend who is working as a truck driver and has Hep C, and he can’t afford it. Even if you bring it down to RM3000 people can’t afford it. The government must help people like this.

Alice, 47, ibu kepada tiga anak.

Saya disahkan menghidap hepatitis C menerusi ujian darah rutin pada tahun 1991. Pada ketika itu, saya bertanya, “Apa itu hepatitis C?”, dan “Mengapa saya?”. Saya berfikir bagaimana agaknya saya telah dijangkiti, dan saya sedar satu-satunya risiko jangkitan saya adalah melalui pemindahan platlet sewaktu saya dirawat untuk demam denggi. Sejak itu, saya mendalami penyakit hepatitis C atas usaha sendiri dan mendapati bahawa doktor rata-rata masih kurang arif tentang rawatan penyakit ini. Kemudiannya saya memulakan rawatan dengan pegylated interferon-ribavirin, dan sepanjang tempoh itu penyakit itu berbalik (relapse) sebanyak lima kali. Pada masa itu jugalah saya berasa tidak terdaya lagi. Namun setelah beberapa kali menempuhi dugaan relapse, saya nekad: Kehidupan mesti diteruskan! Lantas saya merancang untuk berumahtangga dan mempunyai anak antara sesi rawatan.

Selepas itu, ubat rawatan hepatitis C jenis DAA mula diperkenalkan, namun tidak didapati di sini. Pada tahun 2015, saya ke luar negara untuk mendapatkan rawatan walaupun kosnya mahal, saya kini telah sembuh. Saya percaya saya telah pulih sepenuhnya. Rawatan itu telah menyelamatkan nyawa saya. Namun begitu, saya terfikir, saya mampu mendapatkan rawatan tetapi ramai lagi orang yang senasib dengan saya yang langsung tidak berkemampuan, seperti rakan saya yang bekerja sebagai pemandu lori. Sekalipun harga ubat diturunkan kepada RM3,000, masih terlalu ramai yang tidak mampu. Kerajaan seharusnya membantu golongan yang memerlukan seperti mereka ini.



Mohd Ramlan bin Abdul Rani

54, self-employed (small business), father of three children

In 1999, I vomited blood and decided to go to my panel hospital to get a check up, and it was then that I was diagnosed with HCV. I realised that the only way I could have contracted this disease was through blood transfusions I underwent during an angioplasty in 1983. I became really stressed, lost self-esteem, and this took a major toll on my work performance.

I've undergone treatment multiple times, beginning in 1999 with pegylated interferon-ribavirin. In 2000, I achieved SVR²⁷⁹ so I stopped treatment. Then in 2008 I vomited blood again, and found out that my disease has relapsed. Not only that, I discovered that my cirrhosis was at Stage B, meaning that it was beginning to decompensate.²⁸⁰

I requested to be part of the DNDi clinical trial, but the doctor said because I've got decompensated cirrhosis, I couldn't. My only hope is a liver transplant.

About the price of DAAs, I might as well go and buy a Toyota Vios! It's too high. I would prefer if they make generics in Malaysia. We have the capabilities. We have Pharmaniaga. They can do it. It's okay if Gilead wants to take royalties from us.²⁸¹ We should do it just like they did it in India. USD \$84,000 – you can feed an entire village!

Mohd Ramlan bin Abdul Rani, 54, bekerja sendiri (perniagaan kecil), bapa kepada tiga orang anak

Pada tahun 1999, saya muntah darah dan menjalani pemeriksaan di hospital panel di mana saya disahkan menghidapi HCV. Saya sedar bahawa satu-satunya cara saya dijangkiti penyakit ini adalah melalui pemindahan darah yang saya terima untuk prosedur angioplasti pada tahun 1983. Saya telah mengalami tekanan dan kehilangan keyakinan diri sehingga menjejaskan prestasi kerja saya.

Saya telah menjalani beberapa rawatan dengan pegylated interferon-ribavirin bermula pada tahun yang sama. Setahun kemudian, saya menghentikan rawatan itu kerana saya mencapai tahap SVR (sembuh). Malangnya, pada tahun 2008, saya muntah darah semula dan mendapati penyakit saya telah kembali. Bukan itu sahaja, sirosis saya berada pada Peringkat B di mana hati saya telah mula mengalami dekompensasi (rosak).

Saya memohon untuk menyertai percubaan klinikal DNDi tetapi permohonan saya ditolak oleh doktor atas sebab tahap sirosis saya. Satu-satunya harapan untuk saya sembuh adalah melalui pemindahan hati..

Berkaitan harga DAA, saya lebih rela beli kereta Toyota Vios! Harga yang disyorkan kepada kerajaan sangat tinggi. Pada pendapat saya, Malaysia berkemampuan untuk menghasilkan ubat generik HCV melalui syarikat farmaseutikal tempatan seperti Pharmaniaga. Kalau terpaksa membayar royalti kepada Gilead pun tak mengapa. Malaysia harus mencontohi langkah yang diambil oleh India dalam menangani isu ubat-ubatan HCV. Dengan harga setinggi USD \$84,000, kita boleh menanggung makanan untuk satu kampung!

279 Sustained virological response, a surrogate marker for a HCV cure.

280 i.e. that there were clinically evident complications.

281 The issuance of a compulsory license (government use license) would enable the government to either import or locally produce generics for the domestic market, and they would pay Gilead royalties.



Jasni bin Abdul Razak
51, former soldier, father of
two children (DNDi clinical
trial participant)

It was Ramadan last year (2015) when I got diagnosed with HCV. I'd vomited blood, and it wasn't stale blood. It was bright red. Turns out I'd already started bleeding inside and my liver was swollen. I was already in the early stages of cirrhosis.

When the doctors first told me about my condition, I was worried and wanted to know, how did I get this hepatitis C? My wife has always been very supportive. She read about it on the Internet and explained to me. The doctor later told me that in my case, I could have contracted HCV through a blood transfusion. I was hospitalised twice in my life due to an arm injury in the early 90s and an accident in 2003. I became more worried because in the recent years, I have regularly donated blood. I donated all the time. I completely stopped this since finding out about my HCV.

After the diagnosis, Dr Tee told me about a clinical trial that uses DAAs, which has a 90 per cent cure rate. My immediate concern was whether I could continue working in the steel company I work in, but Dr Tee advised me to avoid strenuous activity. So I quit my job.

Today is my first day taking the DAA medicine. I am very grateful to be part of the clinical trial but I wonder what would happen to others who are less fortunate. The prices of these drugs are very expensive. For people who can afford it, that's fine. But what about people like us, the village people who raise up the country's economy? I think the government must do something to help the working class like me. We didn't ask for this disease and we simply can't afford the treatment.

**Jasni bin Abdul Razak, 51, bekas tentera, ayah kepada dua orang anak
(Peserta percubaan klinikal DNDi)**

Saya disahkan menghidap HCV pada bulan Ramadan tahun lepas (2015). Saya muntah darah merah, bukan darah hitam. Rupa-rupanya, saya mengalami pendarahan dalaman and hati saya telah bengkak. Saya berada di tahap awal sirosis.

Apabila doktor memaklumkan keadaan penyakit saya, saya risau dan ingin tahu bagaimana saya boleh mendapat penyakit ini. Isteri saya banyak memberikan sokongan kepada saya. Dia membuat carian tentang penyakit HCV di Internet dan menerangkan kepada saya. Doktor juga kemudiannya memberitahu saya bahawa kemungkinan besar saya mendapat penyakit ini menerusi pemindahan darah. Sepanjang hidup saya, saya pernah dimasukkan ke wad sebanyak dua kali. Kali pertama disebabkan kecederaan pada lengan yang serius pada awal tahun 90-an dan kedua disebabkan kemalangan pada tahun 2003. Saya bertambah risau kerana sejak beberapa tahun kebelakangan ini saya kerap menderma darah. Namun sekarang saya telah berhenti menderma darah.

Selepas disahkan HCV, Dr Tee memberitahu saya tentang percubaan klinikal rawatan menggunakan DAA yang mempunyai kadar penyembuhan 90 peratus. Saya risau, jika saya menjalani rawatan ini, dapatkah saya meneruskan pekerjaan saya di kilang besi? Doktor Tee menasihati saya untuk mengelakkan kerja-kerja yang berat. Oleh itu, saya membuat keputusan untuk berhenti kerja.

Ini hari pertama saya mengambil ubat DAA. Saya bersyukur kerana dapat menyertai percubaan klinikal tetapi terfikir juga tentang pesakit lain yang kurang bernasib baik. Harga ubat-ubatan DAA ini terlampau mahal. Bagi yang berkemampuan, harga ini mungkin tidak menjadi masalah. Tetapi bagaimana pula dengan orang kampung macam saya? Kami juga menyumbang kepada ekonomi negara? Kerajaan harus melakukan sesuatu untuk membantu golongan perkerja seperti saya. Kami tidak meminta penyakit ini dan kami memang tidak mampu untuk menanggung kos perubatan.



Lin*, 41
41, mother of two children,
HIV-co-infected

In 2005, I had some symptoms of jaundice so I went to seek treatment in a nearby hospital. My health condition turned out to be more serious than I expected. I was diagnosed with HCV and HIV.

I didn't know what to say. I was shocked and enraged, and filled with despair because I didn't know how I could have contracted these diseases. After discussing risk factors and my lifestyle with my doctor, we concluded that I may have contracted them from my late husband who may have been an injection drug user.

I started HIV treatment in 2005, right after my diagnosis. It wasn't until 2014 that I started treatment with Pegasys (pegylated interferon) and ribavirin, but I had to stop the treatment because I started developing mouth ulcers and just had a really bad reaction to the medication.

I am not sure how long I will live. I really hope I get to take DAAs. I hope the government can help. Because if they ask me to buy it, I wouldn't be able to afford it.

Lin, 41, ibu kepada dua orang anak, pesakit HIV/HCV

Pada tahun 2005, saya telah mengalami beberapa simptom penyakit demam kuning. Lantas, saya mendapatkan rawatan di hospital berdekatan. Malangnya, keadaan kesihatan saya lebih serius daripada jangkaan saya. Saya disahkan menghidap HCV dan HIV.

Pada ketika itu saya terdiam. Saya terperanjat, marah, dan hampir berputus asa kerana saya betul-betul tidak tahu bagaimana saya boleh mendapat penyakit ini. Selepas berbincang mengenai faktor-faktor risiko dan gaya hidup saya dengan doktor, saya sedar bahawa saya mungkin mendapat kedua-dua penyakit ini daripada arwah suami saya yang mungkin seorang pengguna dadah suntikan.

Saya memulakan rawatan HIV saya sejurus selepas diagnosis. Saya hanya memulakan rawatan Pegasys (pegylated interferon) dan ribavirin pada tahun 2014, tetapi saya terpaksa berhenti kerana mengalami ulser mulut dan reaksi lain yang teruk terhadap rawatan tersebut.

Saya tidak pasti berapa lama saya akan hidup, namun saya berharap saya dapat mencuba DAA. Saya juga berharap kerajaan dapat membantu saya kerana tanpa bantuan kerajaan saya tidak mampu membelinya.

* Upon patient's request, the patient's name is changed to protect her identity.

* Atas permintaan pesakit, namanya dirahsiakan untuk melindungi identiti.



Wailinah binti Alok
57, housewife, mother of three

I regularly donated blood until I got a call from the Queen Elizabeth Hospital's blood bank in 2014. They told me that I have got HCV. I was so surprised. I knew that the only way I could've contracted HCV was through a blood transfusion I received during my Caesarean section I had in 1987.

Initially I went to Keningau hospital to seek treatment. Later, I was directed to Queen Elizabeth Hospital in Kota Kinabalu for my check-ups. The doctors here told me that I need to go to Selayang hospital but I could not afford to travel there. I was lucky though, that the welfare department covered my expenses to Selayang Hospital.

It was at Selayang Hospital that I was told I had decompensated cirrhosis. I'm now being treated with Pegasys (pegylated interferon) and ribavirin for a 48-week course and I've got 36 weeks to go. The side effects are horrible. I have a swollen throat and palate, and bleeding gums. Because of my cirrhosis sometimes I cough up blood.

I really want to try these DAAs but I can't afford them. I usually spend about RM 1,000 monthly because every week I have to travel to Kota Kinabalu for my HCV treatment. I am just a fruit and vegetable farmer. My income is meagre, and I have no savings. These DAAs are good, right? I've only just found out about them and I think the government should offer them to us.

Wailinah binti Alok, 57, suri rumah, ibu kepada tiga orang anak

Saya selalu menderma darah sehinggalah saya mendapat panggilan daripada bank darah Hospital Queen Elizabeth pada tahun 2014 yang mengesahkan saya menghidap HCV. Saya amat terkejut namun sedar bahawa saya mungkin telah dijangkiti HCV menerusi pemindahan darah sewaktu pembedahan Caesarean saya pada tahun 1987.

Pada mulanya, saya mendapatkan rawatan HCV di Hospital Keningau. Kemudian, saya diarahkan untuk mendapatkan rawatan di Hospital Queen Elizabeth, Kota Kinabalu untuk pemeriksaan susulan. Doktor-doktor di sini pula memberitahu saya untuk pergi ke Hospital Selayang di Kuala Lumpur untuk meneruskan rawatan, tetapi saya tidak mampu untuk ke sana. Namun begitu, saya bertuah kerana kos perjalanan saya ke Hospital Selayang ditanggung oleh pihak Jabatan Kebajikan Masyarakat.

Di Hospital Selayang, saya diberitahu bahawa saya mula mengalami sirosis dekompensasi. Sekarang, saya sedang menjalani rawatan Pegasys (pegylated interferon) dan ribavirin untuk 48 minggu. Saya masih perlu menjalani rawatan untuk 36 minggu lagi. Kesan-kesan sampingan adalah amat teruk. Tekak dan lelangit saya bengkak. Gusi saya berdarah. Kadang-kala, saya batuk darah disebabkan sirosis.

Saya betul-betul ingin mencuba ubat-ubatan DAA ini tetapi saya tidak mampu. Perbelanjaan bulanan saya mencecah RM1,000 kerana setiap minggu saya perlu berulang-alik dari Keningau ke Kota Kinabalu untuk mendapatkan rawatan HCV. Saya cuma seorang petani buah-buahan dan sayur-sayuran secara kecil-kecilan. Pendapatan saya tidak seberapa and saya tidak mempunyai sebarang simpanan. Ubat-ubatan DAA ini baik, bukan? Saya baru mendapat tahu tentang ubat ini dan saya rasa kerajaan harus menawarkan ubat-ubatan ini kepada kami.



Linda Wong Mui Nyuk
61, retired nurse, married

I have SLE (systemic lupus erythematosus), and I discovered that I had HCV when I was being screened for a SLE clinical trial in 2010. I was diagnosed with HCV genotype 1, which I think I must've contracted during a series of blood transfusions I had for SLE treatment during the early 1980s.

In addition to HCV and SLE, I have hyperthyroidism and high cholesterol.

In March 2016, I participated in a clinical trial with Viekirax and so got DAAs. After just three months, I was cured! I am very happy now but I am still on other medications for my other diseases. DAAs are definitely expensive. Every HCV patient needs to be treated and I think the government should form a special team to look into this matter and devise ways to treat the HCV patients in this country so we they can keep functioning and contributing to the society.

Linda Wong Mui Nyuk, 61, pesara jururawat, berkahwin

Saya penghidap SLE (penyakit lupus). Pada tahun 2010, saya mendapat tahu bahawa saya juga menghidap HCV apabila saya menjalani ujian saringan untuk percubaan klinikal SLE. Saya disahkan menghidap HCV genotaip 1 yang mungkin berjangkit melalui salah satu pemindahan darah untuk rawatan SLE saya pada awal tahun 1980an.

Selain HCV dan SLE, saya juga mengalami penyakit tiroid dan tahap kolesterol tinggi.

Pada bulan Mac 2016, saya menyertai satu percubaan klinikal dengan Viekirax dan diberikan ubat-ubatan DAA. Selepas tiga bulan, saya telah sembuh! Saya amat gembira tetapi saya masih mengambil ubat-ubat lain untuk penyakit saya yang lain. DAA memang mahal. Setiap pesakit HCV harus dirawat dan saya rasa kerajaan perlu membentuk satu pasukan khas yang dapat meneliti perkara ini dan merangka langkah-langkah bagi merawat para pesakit HCV di negara ini agar mereka dapat menjalani kehidupan yang normal dan menyumbang kepada masyarakat.



Mohd Affarizal bin Othman
36, employed, methadone client, father of three

I was first diagnosed with HCV in 2014 at the methadone clinic. If I hadn't joined this (methadone) programme, I probably would have never known anything about my condition. As far as I know, HCV doesn't show symptoms for 8-10 years. That said, I haven't asked my doctor in detail about this disease because it makes me panic. So what I know, I know from reading posters. I'd be happy to attend awareness programmes on HCV.

I can't afford DAAs. If I had RM52,000 (USD \$12,000), I would rather spend it on my family. If I am meant to die because of HCV, then let it be. It is up to the government if they want to help drug users like me because we simply can't afford the treatment.

Mohd Affarizal bin Othman, 36, berkerja, klien metadon, bapa kepada tiga orang anak, klien methadone

Saya disahkan menghidap HCV pada tahun 2014 di klinik metadon. Kalau saya tak menyertai program (metadon) ini, saya mungkin tidak akan tahu tentang keadaan kesihatan saya. Setahu saya, HCV tidak menunjukkan sebarang simtom untuk 8-10 tahun. Namun begitu, saya tidak pernah bertanya dengan doktor saya secara terperinci tentang penyakit ini kerana saya cepat panik. Sumber pengetahuan saya ialah poster-poster HCV yang saya baca dan lihat. Saya berminat untuk menghadiri program-program kesedaran HCV.

Saya tidak mampu membeli ubat-ubatan DAA. Jikalau saya mempunyai RM 52,000 (USD \$12,000), saya lebih rela membelanjakan duit itu untuk keluarga saya. Kalau saya ditakdirkan untuk mati kerana HCV, saya redha. Terpulang kepada kerajaan jika mereka nak membantu golongan pengguna dadah macam saya kerana kami sememangnya tidak mampu untuk menanggung kos rawatan.



Nordin bin Kasmani
62, former soldier, father of
four, methadone client

I was diagnosed with HCV when I went to the National Heart Institute (IJN) for my heart attack in 2012. As a former injecting drug user, I wasn't really surprised when they told me about my HCV. The doctor told me that the treatment for HCV would cost me a fortune. So I had to choose between my heart and HCV treatment. I opted for the heart treatment because at that time I'd previously had two heart attacks.

I know that HCV is a silent killer. I want to get treated but I simply can't afford to. I'm unemployed at the moment and it is very difficult for me to get a job because of the community's perception towards former drug users. I only get RM230 (USD \$52) per month from the welfare department, and this is just enough to cover my expenses to travel to and fro from the methadone clinic.

For now, all I can do is to try to have healthy lifestyle and a balanced diet to manage my HCV. If the government can help or if there are NGOs who can raise this issue with the government, I'm sure the government can fight this disease. Who doesn't want to get cured, right? Everyone wants to. It just comes down to cost.

Nordin bin Kasmani, 62, bekas anggota tentera, klien metadon

Saya disahkan menghidap HCV sewaktu menjalani rawatan di Institut Jantung Negara (IJN) untuk serangan jantung pada tahun 2012. Sebagai seorang bekas pengguna dadah suntikan, saya tidak terkejut apabila disahkan HCV. Doktor memberitahu saya bahawa rawatan untuk HCV saya akan menelan perbelanjaan yang besar. Oleh itu, saya terpaksa memilih antara rawatan jantung dan HCV. Pada masa itu, saya memilih rawatan jantung kerana sebelum itu saya sudahpun mengalami serangan jantung sebanyak dua kali.

Saya tahu bahawa HCV adalah pembunuh senyap. Saya ingin mendapatkan rawatan tetapi saya tidak mampu. Sekarang saya tidak berkerja dan amat sukar untuk saya mendapatkan kerja disebabkan oleh persepsi masyarakat yang negatif terhadap bekas pengguna dadah. Saya cuma menerima RM230 (USD \$52) sebulan daripada Jabatan Kebajikan Masyarakat yang hanya cukup untuk saya berulang-alik dari rumah ke klinik metadon.

Pada masa ini, saya hanya mampu untuk mengamalkan gaya hidup yang sihat dan pemakanan yang seimbang bagi mengelakkan penyakit HCV saya melarat. Sekiranya kerajaan hendak membantu atau ada pertubuhan-pertubuhan bukan kerajaan (NGO) yang boleh mengemukakan isu ini kepada kerajaan, saya pasti kerajaan dapat menangani penyakit ini sebanik-baiknya. Siapa yang tidak mahu sembuh, bukan? Namun itu semua bergantung kepada kos rawatan.



Suhaimi bin Talib
49, unemployed, HIV/HCV co-
infected, methadone client

I was diagnosed with HIV in 2006. I was just sitting at home and suddenly felt shortness of breath. I was rushed to a nearby hospital and the doctors did some blood tests and X-rays. The test results came back for positive for HIV and showed my CD4 count was 100. I could not afford anti-retroviral (ARV) treatment. I get free medication from the government. In the past, I have been also hospitalised due to tuberculosis.

What is HCV? I don't know. I just got to know about HCV from my last doctor's appointment at the methadone clinic. I could have contracted this disease from sharing needles. I am not sure if the disease is deadly but I will just follow the doctor's instructions. Currently, I am only taking the ART medicine and some vitamins for general health.

DAA's are too expensive and many cannot afford them. I can't afford it because I am only helping my sister at her restaurant, so I don't make much money. I think the government should take the same approach as it took for ARV in order to eliminate HCV. In the long run, ARV medicines might even be more expensive compared to DAA's because you have to take ARV for your entire life.

Suhaimi bin Talib, 49, tidak berkerja, pesakit HIV/ HCV, klien metadon

Saya disahkan HIV pada tahun 2006. Pada masa itu, saya berada di rumah apabila tiba-tiba saya sesak nafas. Saya dikejarkan ke hospital berhampiran dan doktor-doktor di sana melakukan beberapa ujian darah dan sinar-x. Keputusan ujian darah menunjukkan saya HIV positif dan kiraan CD4 saya cuma 100. Saya tidak mampu menjalani rawatan antiretroviral (ARV). Saya diberikan ubat ini secara percuma oleh pihak kerajaan. Satu ketika dahulu saya juga pernah dimasukkan ke hospital kerana tibi.

Apa itu HCV? Saya tak tahu. Saya hanya mendapat tahu tentang penyakit HCV daripada doktor di klinik metadon. Saya mungkin dijangkiti akibat perkongsian jarum suntikan dadah. Saya tak pasti jika penyakit ini berbahaya tapi saya akan mengikut arahan doktor. Sekarang, saya mengambil ubat ARV dan beberapa pil vitamin untuk kesihatan saya.

Ubat-ubatan DAA terlampau mahal dan ramai tidak mampu untuk mendapatkannya. Saya tidak berkemampuan kerana saya cuma membantu kakak saya di restorannya. Pendapatan saya rendah. Saya rasa kerajaan harus mengulang langkah yang sama seperti pemberian rawatan ARV secara percuma dalam membanteras penyakit HCV ini. Dalam jangka masa panjang, kos rawatan ARV mungkin lebih mahal daripada DAA kerana ubat-ubatan ARV perlu diambil sepanjang hayat.

Chapter 8:

Opportunities, barriers, and the way forward: perspectives of Malaysian clinicians, service providers, and other stakeholders

Compiled by Shangeetha Thirumayni



Dr Tan Soek Siam
 Consultant Hepatologist
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At present, anti-HCV is widely available as a tool for HCV screening however there are limited resources dedicated to HCV diagnostics like HCVRNA and HCV genotype, which presents a sizeable barrier to getting people into care. In addition, we don't know whether we should screen only those with risk factors. Well-designed studies in our local population would really help us in this and not missing patients who can potentially be cured with effective treatment. Moreover opportunity to pick up at risk cases when they come for any medical care in our health care facilities maybe missed as clinicians don't necessarily have the time to go through entire risk histories with patients or patients may not be willing to divulge some of the information. Hence I feel education of the public on the risk for HCV transmission and empowering them to ask for hepatitis C screening will help to close the gap. Raising public awareness and reducing the stigma of viral hepatitis would be some of the things that the NGO and patient support groups could do. In the clinical scenario as is, there are also structural barriers to getting patients into care. Some patients who are HCV seropositive undergo ALT (alanine aminotransferase) tests (Liver Function Tests) and get filtered out if normal at the primary healthcare level, so they don't get referred to me. There, the linkage to care is interrupted. We need to find solutions to this. We need to train more health care workers starting from the point of screening to diagnosis to referral and eventually to the management of hepatitis C cases. Having this at the ground level, escalation of treatment to more people living with HCV may work with a well run referral pathway and a network system to connect the liver experts to more treating clinicians in various parts of the country. In terms of scaling up diagnostics, I think we need to scale up screening and diagnosis of active infection in community health clinics (*klinik kesihatan*). We've also got to explore the role of NGOs in this process – rapid tests at NGO facilities can really help. Once we have an affordable pan-genotypic DAA regimen as the primary therapy for HCV, genotype tests may not be necessary, and as a result, we would have a simplified diagnostics and management pathway and cost savings for the stakeholders.

I talked earlier about the need to collect detailed risk histories, and the time needed to ascertain potential adherence and compliance to the DAAs. Peer educators or peer facilitators could potentially be very useful in this scenario.

In terms of DAAs, my favourite thing about them has to be the high response rate. With pegylated interferon-ribavirin, there's a lot of health care support and facilities that is needed to keep patients in treatment. With the shorter time period and less side effects in treatment with DAAs, a lot of this is eliminated. Finally, my thoughts about the expensive DAA prices: there are two options in my mind: co-payments that are based on patient income levels, or affordable prices through special licences/negotiation. The proposed prices for branded DAAs are simply too expensive for our healthcare budget to bear.



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In regard to diagnostics, the key obstacles to achieving the WHO targets in 2020 and 2030 are the high cost and the limited availability of HCV tests which are required for confirmation of active infection, which are simply out of reach of the patients who need it. However, there are several developments or opportunities that indicate that this will change. On the 13th of January 2016, via a Facebook post, the Director-General of Health Datuk Dr Noor Hisham Abdullah expressed his commitment to a 'public health approach to Hepatitis C within the framework of the future National Strategic Plan on Viral Hepatitis'.²⁸² The Minister of Health expressed a similar commitment the previous year, emphasising the need to focus on the population at risk such as people who inject drugs in Malaysia's Intervention Note to the WHO Regional Committee meeting in 2015.²⁸³

As a clinician, I think that we simply don't have enough awareness and that's why HCV diagnosis is estimated to be extremely low. Raising awareness, scaling-up HCV detection, strengthening prevention, enhancing linkage to care and treatment should be part of a comprehensive national plan for hepatitis C.

In terms of treatment, DAAs are a major advancement in the evolution of HCV therapy. They are potent inhibitors of HCV replication and they achieve very high cure rates with a short duration of treatment. DAA combinations mean that interferon-free therapy is now a reality. However, access to DAAs remains a real challenge.

The key problem with Malaysia is that we've got a high HCV prevalence with a rising disease burden. We need to work in partnership with relevant stakeholders to facilitate the development of a strategic roadmap to drive the HCV response here, and that strategy should, among other things, contain a standardised algorithm to enhance HCV diagnosis, incorporate a comprehensive surveillance strategy, and should be costed to achieve the 2020 interim and 2030 elimination targets set by WHO.



**Datuk Dr Raman A/L
Muthukaruppan Chettiar**
Head of Gastroenterologist,
Queen Elizabeth Hospital, Kota
Kinabalu, Sabah

Despite the increasing burden of HCV, resources allocated to the diagnostics are inadequate, which presents a major challenge in getting people to come forward for screening. I think the government via Ministry of Health (MOH) should be the driving factor in scaling up the diagnostic settings in Malaysia.

In my view, the current number of allocated pegylated interferon and ribavirin treatments allocated to Sabah is satisfactory but the various demographic factors influencing who should be treated presents a challenge for us as doctors because we need to carefully select the most eligible patient in these cases. In earlier days, it used to be better with the availability of TBP (Tabung Bantuan Perubatan/Medical Assistance Fund). More funding is definitely needed to treat patients with cirrhosis, advanced fibrosis and genotype 1 patients who have had failed treatments.

DAAs (direct acting antivirals) are state-of-the-art medications for HCV patients, and they work much better for those with cirrhosis, relapse patients, and genotype 1 patients compared to pegylated interferon/ribavirin. We need DAAs because they will ease treatment and produce high rate of SVR (sustained virologic response) across all genotypes. In my opinion, pegylated interferon and ribavirin should be eventually phased out because of the adverse side effects.

Providing screening services to the high-risk population remains a hurdle because many may fail to follow up due to limited resources, fear, or misunderstanding. Therefore, awareness programmes on HCV and efforts to expand access to HCV services by empowering general practitioners (GP) will bring about a positive difference to the HCV's situation in Malaysia, especially in the rural areas.

282 Abdullah NH. [Facebook post]. 2016 Jan 13 [cited 2016 Oct 24]. Available from: <https://www.facebook.com/DGHisham/posts/1121032567920630>

283 Malaysia's Intervention Note on Viral Hepatitis in the 66th Session of the WPRO Regional Committee Meeting in October 2015. [Internet]. 2015 Oct 16 [cited 2016 Oct 2015]. Available from: <https://kpkeshihatan.com/2015/10/13/malaysias-intervention-note-on-viral-hepatitis-at-the-66th-session-of-wpro-regional-committee-meeting-12-16th-oct-2015/>



Dr Tee Hoi Poh
 Consultant Gastroenterologist
 Tengku Ampuan Afzan Hospital,
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The marketing drive for hepatitis C (HCV) diagnosis is low compared to hepatitis B because there is no vaccine for HCV. As for now, there is no national HCV plan and opportunistic screenings for HCV are limited to a few settings and groups such as drug rehabilitation centers, prisons, and persons receiving opioids substitution therapy. Diagnoses for others are usually done based on physicians' suspicion. I feel that HCV diagnostics should be included in general routine health-screening packages to diagnose more and create awareness among the public. In addition, the diagnosis algorithm should be made simple with reflex testing for HCV viral load for positive serology tests.

The current diagnostic environment can be improved because as for now molecular diagnostic tests (viral load and genotype tests) are only available in two government hospitals: Hospital Kuala Lumpur and Sungai Buloh. Cluster laboratories that offer molecular diagnostic tests could be established to cater for patients all over Malaysia.

We need to devise a HCV national plan that encompasses awareness, screenings, and treatment. As part of this national plan, the Ministry of Health should set up a special task force similar to how they did with HIV/AIDS and set up a designation unit. This unit should be given the autonomy to run anti-hepatitis programmes in the country, targeting high-risk groups, which, provided there is sufficient treatment for the present patients, can eventually reduce the number of new transmissions.

In terms of DAAs, they are definitely the best approach to treat chronic HCV patients. Pegylated interferon with ribavirin is less effective in the cirrhotic cohort. The high SVR rates associated with DAA therapies offers an opportunity for eradication of HCV prevalence cases in this country - if treatment rate exceeds new infections. Besides that, the drug's administration is simpler compared to pegylated interferon. This means it can be used to offer cure for a large number of patients with reduced organisational support, for instance, via the public health approach. In relation to the exorbitant prices of DAAs, the government should allow the use of generic drugs to treat HCV patients or negotiate for special packages with the pharmaceutical company that fits within the national health budget. It is very crucial for the government to step in because currently only a handful of HCV patients are treated with DAAs provided by clinical trials, limited insurance schemes and private sponsorships.



Dr Jayaram Menon
 Consultant Gastroenterologist,
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 Queen Elizabeth Hospital, Kota
 Kinabalu, Sabah

Most people with HCV are unaware of their status because it is usually asymptomatic and often does not come to light until some years after infection. Thus, HCV screening should be included in essential health blood test packages in all-private labs to increase the number of diagnosed people in the country. This will eventually create the awareness on the importance of screening for Hepatitis C amongst the public.

Federal funding for HCV services in east Malaysia has to be dramatically improved to address the needs and priorities of the patients here. There should be a greater and more rapid access to HCV RNA (ribonucleic acid) tests because currently we have to send the blood samples to Sungai Buloh Hospital (West Malaysia) or private labs. More funding is needed to scale up testing with linkage to care and treatment. Perhaps a cluster laboratory can be established in East Malaysia to cater to HCV patients here.

DAAs are definitely the treatment of choice. Our experience with these drugs administered through clinical trials has been very positive. They can be made affordable and accessible akin to the introduction of HAART for HIV. Initiatives to improve the affordability and access to these medicines should be supported to eliminate HCV as a major public health threat.



Dr Sha'ari Bin Ngadiman

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Ministry of Health Malaysia*

As Head of the HIV/STI/Hep C sector in the Malaysian Ministry of Health, I'm focused towards producing the national HCV strategic plan. This is in line with the WHO recommendations, i.e. that each country has national plans to tackle viral hepatitis.

I'm keen to make use of existing HIV infrastructure to integrate some elements of the HCV response. But given that HCV services entail a separate set of challenges, we'll have to do this carefully. Currently, HCV screening services are provided in drug rehabilitation centers, methadone clinics, and prisons. In the national strategic plan, we plan to strengthen this by expanding screening to these facilities. Besides that, the current AIDS surveillance system can include hepatitis C to monitor the epidemic's progression in the country.

In order for Malaysia to achieve the WPRO target of 30% of eligible persons diagnosed by 2020, we definitely need to devise a short and medium term plan on hepatitis C. These plans should reflect the whole continuum of HCV services – from preventing and reducing transmission, diagnosing infection, through to providing sufficient number of treatments for HCV patients. Meanwhile, the advocacy voice provided by patients and non-governmental organisations can increase the priority on the need to eliminate HCV as a major public health threat.



Dr Norsiah Ali

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In the sphere of HCV diagnostics among people who inject drugs (PWID) under the national harm reduction programmes, we have no issues in screening them because the diagnostics services are extended to prisons, methadone services, and drug rehabilitation centers. Nowadays, clients taking the government-supplied methadone from private clinics are entitled for free screening as their blood samples can be sent to the nearest government hospital's laboratory. However, some private methadone clients miss the screening opportunity because they cannot afford the screening tests. Some of the high-risk groups often do not come forward for the HCV screenings because lack of awareness and stigma. Therefore, it is essential for the stakeholders to create awareness about HCV in the media.

As a clinician, I feel there is an unaddressed need that needs to be met in the area of HCV treatment because methadone clients with HCV are often considered as the low priority group due to their high-risk behaviour and complications. Thus, over the years, many of them have died due to HCV complications compared to HIV, tuberculosis, and other external factors. Currently, methadone, anti tuberculosis and antiretroviral treatments are given free to them. I hope there is a linkage of service in the continuum of public health services for HCV methadone clients. There has been an increase in the number of HCV methadone clients receiving HCV treatment but the figure is negligible.

The new generation of the DAAs have higher cure rates and lower side effects compared to pegylated interferon-ribavirin but the prices are exorbitant. Given the current situation, perhaps the government could initially allocate a small number of treatments for PWIDs. In the long run, however, if we're looking at a sustainable plan, the government has to introduce generics. Similar approaches used in combating HIV can be used to eliminate HCV as public health threat.



MTAAG+ was established on 21 Dec 2005, and began with advocacy against the proposed Malaysia-U.S. free trade agreement (FTA) and all the intellectual property provisions therein. This is because they strengthen regulatory monopolies and patents for large pharmaceutical companies while reducing the availability of cheaper, generic alternatives for patients. This work continued with advocacy against IP provisions in the Trans-Pacific Partnership (TPP). We work very closely with Third World Network on IP areas on market access to medicines for HIV patients who are co-infected with HCV.

As of now, MTAAG+ has organised four (4) nationwide campaigns aimed at providing HCV tests to the general public. The screening campaigns focus on strategies to identify HCV risk groups hidden in the general population. So far, we have tested 92 people and 45 of them are HCV positive. During our campaigns, we use rapid tests for diagnosis and they cost about RM6.50 per test kit. The uptake of screenings has been positive, and we've been able to educate these communities on HCV prevention, transmission, and treatment.

In 2009, a study has estimated that there are about 500,000 people living with HCV.²⁸⁴ Due to the asymptomatic nature of the disease, many people may not know their status. Thus, it is very important for us to continue our efforts at diagnosing more people. We also need to introduce DAAs to HCV patients because they have higher cure rates, and this can stop new transmissions.

Edward Low

Director
 Positive Malaysian Treatment
 Access & Advocacy Group
 (MTAAG+)



Frederick Pour

Manager, PTF Community Health
 Care Centre
 Sentul, Kuala Lumpur

CHCC is PTF's community healthcare center where we provide healthcare and support to general public, especially to high-risk groups. We provide three (3) types of services in our center, counseling-therapy, which includes face to face and telephone counseling, VCT (voluntary counseling and testing) and outreach programmes. During VCT, clients' identities are anonymous and we provide comprehensive referrals when necessary.

HCV testing is included in our continuum of services because there has been an increase in the demand for HCV diagnostics from the local community. We actively promote testing for HCV and we educate clients on the prevention and transmission of HCV when they come for their testing. With these efforts, we have received positive feedback and uptake because with testing, clients realise the importance of identifying acute cases of HCV. Currently, we are using Chembio and SD HCV antibody rapid test kits at our center. They are offered at the price of RM30 (USD \$6.70), which includes pre- and post-test counseling, referrals to relevant hospitals/ clinics, and follow-up.

Once MOH introduces its imminent viral hepatitis plan, we hope we will be able to direct more HCV-positive clients, especially the ones from the high-risk groups, to accessible and affordable centers for medication and treatment.

284 McDonald SA, Mohamed R, Dahlui M, Naning H, Kamarulzaman A. Bridging the data gaps in the epidemiology of hepatitis C virus infection in Malaysia using multi-parameter evidence synthesis. BMC infectious diseases. 2014 Nov 7; [cited 2016 Oct 18]14(1):1. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25377240282>

Recommendations

| | |
|---|---|
| 1 | Transparency on costs of diagnostics. A disaggregated breakdown is needed on costs of actual reagents versus lab running costs and profit. |
| 2 | Review and increase the strictness of patentability standards and quality of patent application examination to prevent weak patents and the evergreening of patents. |
| 3 | Provide for pre-grant patent opposition in the Patents Act, with appropriate administrative mechanisms. |
| 4 | Put in place administrative mechanisms for patent invalidation (instead of the High Court at the first instance). |
| 5 | Reject TRIPS-plus provisions in trade agreements, including the Regional Comprehensive Economic Partnership (RCEP) under negotiations. |
| 6 | Refrain from implementing TRIPS-plus provisions in the Trans Pacific Partnership Agreement (TPPA) which will not enter into force under the current US government. |
| 7 | Exercise Malaysia's right under international law to issue compulsory licences for sofosbuvir and other drugs that are beyond the Malaysian government's pecuniary reach. |
| 8 | Patient consultation and involvement in the drafting of HCV guidelines. |

Annex

Annex 1: Letter from U.S. Department of State to Andrew Goldman, Knowledge Ecology International affirming the right of States to use TRIPS flexibilities



United States Department of State
 Washington, D.C. 20520

August 5, 2016

Andrew S. Goldman
 Counsel, Policy, and Legal Affairs
 Knowledge Ecology International
 Washington DC

Dear Mr. Goldman:

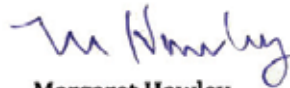
Thank you for your letter of July 20 concerning State Department views on intellectual property (IP) issues related to the UN High Level Panel (UNHLP) on Access to Medicines, as well as to Colombia and India.

The State Department appreciates the UN Secretary General's long-standing focus on health care issues and his goal of expanding access to medicines. We share these interests, and are committed to finding solutions to these complex issues. As the UNHLP on Access to Medicines has not issued its report, we cannot comment on it except to affirm the U.S. submission to the Panel referenced in your letter represents the views of the U.S. government. Given the complex and multifaceted challenge and the need for continued medicines innovation, we do not favor single global solutions. Rather, we are strongly committed to working with all sectors and partners in the context of differing national circumstances and health systems.

As affirmed in the Doha Declaration on the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), the State Department, with the rest of the U.S. government, respects all our trading partners' rights to protect public health and, in particular, to promote access to medicines for all. As your letter noted, this long-standing position was most recently reaffirmed in the United States Trade Representative's 2016 Special 301 Report. The TRIPS Agreement affords countries sufficient flexibility to address serious public health challenges, including the right to issue compulsory licenses for pharmaceuticals in cases that meet all of the elements of Article 31 of TRIPS. We respect such rights when exercised in a manner consistent with TRIPS. We firmly believe countries can address public health challenges while promoting innovation through strong intellectual property rights regimes.

The State Department will continue to promote the above-noted views precisely because we share the interest of the UN Secretary General, and of all countries, in providing adequate access to safe, effective, and affordable medicines to all peoples.

Sincerely,



Margaret Hawley
Deputy Special Representative
Commercial & Business Affairs

IPE/ State Department

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