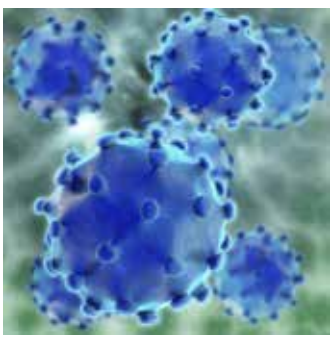
AN ALTERNATIVE RESEARCH AND DEVELOPMENT STRATEGY TO DELIVER AFFORDABLE TREATMENTS FOR HEPATITIS C PATIENTS

The Drugs for Neglected Diseases *initiative*'s hepatitis C drug development strategy based on *patient needs*, not *profits*




APRIL 2016

DNDi
Drugs for Neglected Diseases *initiative*

INTRODUCTION

The Drugs for Neglected Diseases *initiative* (DND*i*) has launched a five-year project to develop affordable treatments for the millions of people suffering from the hepatitis C virus (HCV) who have been neglected by the recent research and development (R&D) revolution for this disease.

The race to approve blockbuster hepatitis C treatments in the United States, Europe, and other high-income countries has not only led to exorbitant drug prices but has also neglected certain patient populations. Under the current R&D model, research has prioritized genotypes that are predominant in high-income markets, and has promoted competition rather than collaboration on development of optimal combinations for public health use.

DND*i* will focus on the creation of a short-course, affordable, easy-to-use, highly efficacious, safe and all-oral pan-genotypic regimen that will enable countries to implement a public health approach to the HCV epidemic.

This approach aims to identify and treat both those in immediate need of therapy, and *all those infected* in order to prevent the long-term morbidity and mortality associated with HCV, as well as decrease further transmission of the virus.

Significant barriers are preventing the vast majority of people with HCV from accessing the powerful new generation of HCV medicines known as direct-acting antivirals (DAAs). DND*i* has entered the HCV field to use a new, "for-patient" approach to R&D to help overcome these barriers and deliver affordable DAAs to those in need.

DND*i* will begin its HCV project with Phase III clinical studies in Malaysia and Thailand to compare sofosbuvir plus the drug candidate ravidasvir with the current standard of care, sofosbuvir plus daclatasvir. DND*i* has concluded agreements to purchase sofosbuvir plus ravidasvir at a price of less than $300 per treatment course for these studies and has secured licensing terms that would make this regimen, if approved, viable as an affordable public health tool at a price of less than $294 per treatment course.

DND*i* will also work to ensure an affordable, quality assured generic source of daclatasvir for its studies and for wider public health use.

CURRENT HCV TREATMENT OPTIONS

Hepatitis C is an inflammatory liver disease caused by infection with HCV, which is transmitted parenterally through exchange of body fluids, mostly through exposure to contaminated blood. About 130-150 million people are chronically infected with HCV and more than 500,000 people are estimated to die from HCV-related liver diseases each year.[1] Most patients are unaware of their HCV infection.

Recent therapeutic breakthroughs in the development of DAAs have made HCV a largely curable condition, but the exorbitant price of these treatments means they are inaccessible to most patients, particularly in countries where the burden of disease is the greatest.

The direct-acting antivirals (DAAs) era

Treatment for HCV has evolved from the use of interferon monotherapy in the 1980s to the use of pegylated interferon, which must be administered through injections and has side effects that are difficult to tolerate. It is only successful 50-80% of the time and must be provided for at least 24 weeks and often up to a year. It is frequently combined with another poorly-tolerated drug, ribavirin.

More recently-approved DAAs over the past three years have revolutionized the HCV therapeutic landscape, with treatments that are significantly more efficacious and better tolerated than interferon-based therapies. The DAA era began with Janssen's (J&J) simeprevir (NS3/4A protease inhibitor). This was followed by Gilead Sciences' (Gilead) sofosbuvir (nucleotide NS5B polymerase inhibitor) in combination with ribavirin with or without pegylated interferon. Sofosbuvir was further developed in combination with daclatasvir (Bristol-Myers Squibb), an NS5A inhibitor, and with ledipasvir, Gilead's own NS5A inhibitor, as a one-tablet fixed-dose combination.[2]

AbbVie has developed and registered its own combination regimen, dasabuvir (NS5B inhibitor), ombitasvir (NS5A inhibitor), paritaprevir (protease inhibitor), and ritonavir. Merck recently received U.S. Food and Drug Administration (FDA) approval on elbasvir (NS5A inhibitor), and grazoprevir (NS3/4A protease inhibitor).

(1) WHO Factsheet No164: Hepatitis C. Accessed April 6, 2016 at http://www.who.int/mediacentre/factsheets/fs164/en/

(2) Lawitz, E., Poordad, F. F., Pang, P. S., Hyland, R. H., Ding, X., Mo, H., Symonds W.T., McHutchison J. G., & Membreno, F. E. (2013). Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *The Lancet*. 2013 Nov 1. pii: S0140-6736(13)62121-2.

Competition for new HCV drugs is fierce and the landscape is changing rapidly as new clinical data are disclosed. Strong financial incentives continue to fuel the rapid advancement of HCV drug R&D.[3,4]

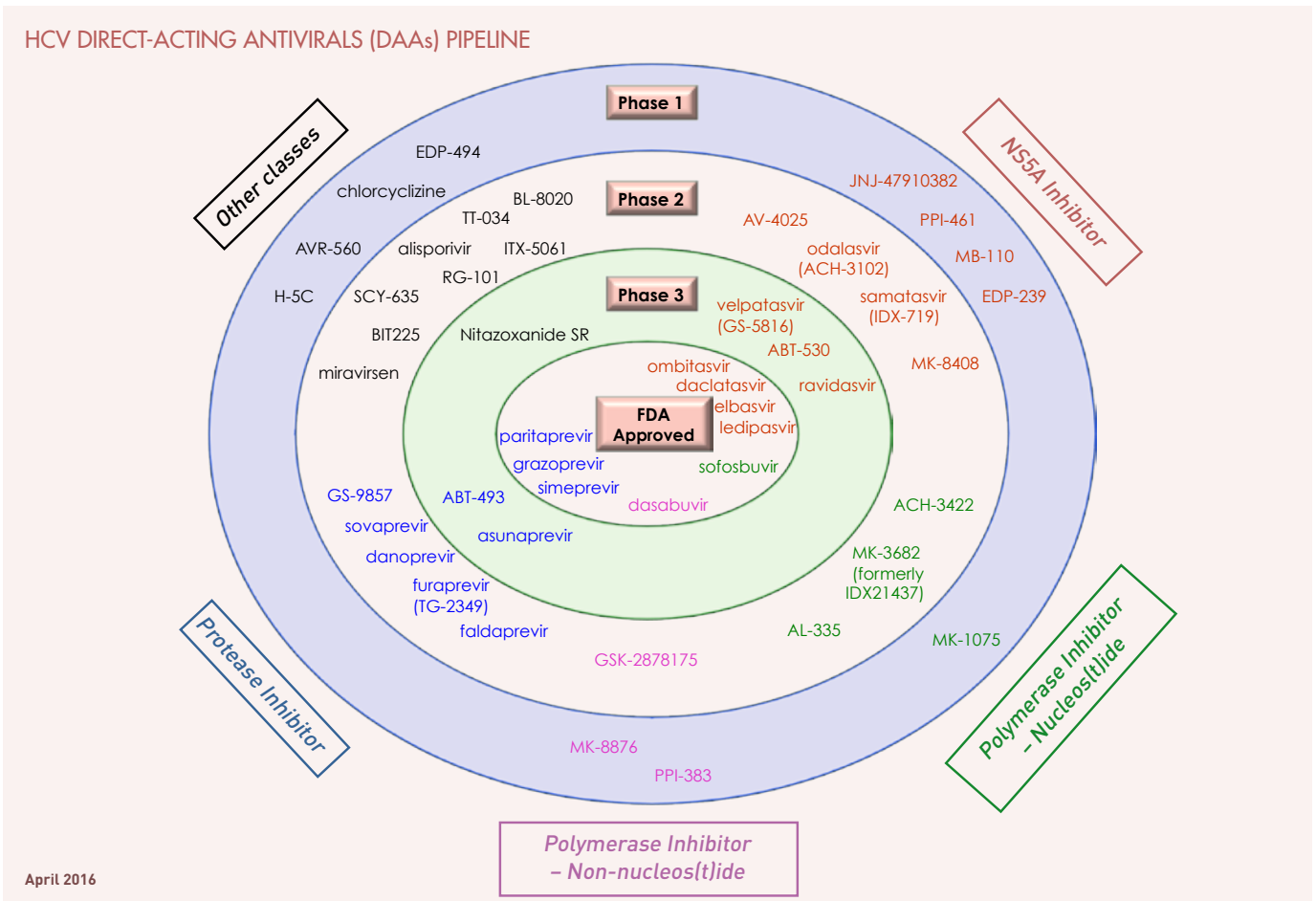
While several protease inhibitors, polymerase inhibitors, and NS5A inhibitors already have been approved in the European Union and/or U.S., including several fixed dose combinations, over 30 agents are still in clinical development.[5,6]

The urgent need for optimal and affordable combinations

There are six genotypes of HCV, and the efficacy of drugs can vary according to the genotype. For example, HCV genotype 3 continues to show inferior response to DAAs relative to genotype 2. DAAs with a high genetic barrier to the development of drug resistance offer hope for the difficult-to-treat groups of patients. More complex combinations involving four or more drugs may be needed.

For HCV patients, a vastly improved therapy that is efficacious, well-tolerated with a short treatment duration, and simple to use (once-daily oral with low pill burden, with less need for on-treatment monitoring) would be ideal. Hopefully more patients, particularly those with advanced liver disease, or co-infection with HIV or hepatitis B virus (HBV), will benefit from further development and optimization of pipeline DAAs.

With HCV-related mortality and morbidity increasing at an accelerated rate,[7,8] we should be racing against the clock to develop optimal new treatments that are affordable in order to ensure that patients, and the health systems that serve them, have equitable access.



(3) Pol, S., Corouge, M., & Sogni, P. (2013) Oral antiviral therapies for chronic hepatitis C infection. *Therapeutic Advances in Infectious Disease.* 1(3), 107-116. (http://tai.sagepub.com/content/1/3/107)
(4) Wendt, A., Adhoute, X., Castellani, P., Oules, V., Ansaldi, C., Benali, S., & Bourlière, M. (2014). Chronic hepatitis C: future treatment. *Clinical pharmacology: advances and applications*, 6, 1.
(5) Clayden, P., Collins, S., Daniels, C., Frick M., Harrington M., Horn T., Jefferys R., Kaplan K., Lessem E., & Swan T. 2013 Pipeline Report, (June 2013 edition; available at http://www.pipelinereport.org; accessed Aug 28, 2013)
(6) Swan, T. (2013). Hepatitis C drug development catapults onward. Accessed at http://www.pipelinereport.org/2013/hcv on Sep 3, 2013
(7) Ward, J. W., Rein, D. B., & Smith, B. D. (2012). Data to Guide the "Test and Treat Era" of Hepatitis C. *Gastroenterology.* 143(4), 887-889.
(8) Deuffic-Burban, S., Deltenre, P., Buti, M., Stroffolini, T., Parkes, J., Mühlberger, N., & Mathurin, P. (2012). Predicted effects of treatment for HCV infection vary among European countries. *Gastroenterology.* 143, 974–985.

BARRIERS TO ACCESSING HCV TREATMENT

HCV is a blood-borne infection, has no known natural non-human reservoir, and is curable. Therefore control or elimination of the disease is a realistic possibility. However, the amazing scientific advances in HCV therapy are not sufficient to enable access for all of those who need treatment.

Prohibitive price of treatments – the US and European case

Historically, pharmaceutical companies price their drugs in high-income countries based on what the market will bear. Although this has been accepted market practice, the exorbitant pricing of HCV therapies has led to treatment rationing and serious consideration of price controls, even in the United States. Gilead's $84,000 price tag for sofosbuvir and $94,500 for the combination of sofosbuvir and ledipasvir has drawn outrage from patients, taxpayers, and lawmakers. In 2014 alone, Medicare and Medicaid spent $5 billion on the combination of sofosbuvir and ledipasvir. This triggered an investigation by the bipartisan Senate Finance Committee, which concluded that "Gilead pursued a calculated scheme for pricing and marketing its HCV drug based on one primary goal, maximizing revenue, regardless of the human consequences."[10]

Governments of some high-income countries, such as France, have negotiated a significantly discounted price for sofosbuvir, but the price tag is still high. France negotiated a price of $47,000[11] per course of treatment of sofosbuvir, but the cost of treating all 814,000 of HCV-infected people in France[12] would be $38 billion. The negotiated price is nearly 10 times the per capita healthcare expenditure in France of $4,864[13]. Even at the discounted price, it would be an extreme financial burden for France to offer access to sofosbuvir to all HCV-infected patients.

GILEAD: $31 BILLION IN REVENUE WITH ONLY 770,000 PATIENTS TREATED

In 2015, Gilead's total revenue worldwide for its HCV products sofosbuvir and sofosbuvir plus lepidasvir was $19.2 billion, with $12.4 billion from the U.S. market. In 2014, its worldwide revenue was $12.4 billion, of which $10.6 was from U.S. sales.

Total revenue for the company for these two years was $31 billion worldwide and $23 billion from the U.S. market alone. Since its launch in 2013, more than 770,000 individuals around the world have been treated with sofosbuvir-based regimens, 400,000 of whom were in the U.S.

More than 3 million HCV-infected individuals in the U.S. have yet to be treated. Therefore, Gilead's potential revenue in the USA market could reach $172.5 billion.[9]

Dr SS Tan, Head of Hepatology Services, Ministry of Health, Malaysia and Head of the Department of Hepatology, Hospital Selayang, Batu caves, Selangor, Malaysia.

"Sofosbuvir has been registered in Malaysia since September 2015 but it is beyond the reach of my patients. It is not available in government hospitals and it is unlikely to be there with the current price tag. As a clinician, it breaks my heart when I am unable to offer my patients such good treatment just because of its exorbitant cost. You should see the shock on my patients' faces when I tell them the price of DAAs."

Barriers to access in low- and middle-income countries

While the exorbitant price of new DAA treatments is exhausting healthcare budgets and leading to treatment rationing in high-income countries, in low- and middle-income countries (LMICs) such prices effectively keep these medicines out of reach of the majority of patients. Eighty five percent (85%) of the world's chronic HCV patients live in LMICs, with 73% in middle-income countries and 12% in low-income countries[14]. High drug prices are now the most significant barrier to overcome in these countries.

(9) Gilead Sciences (GILD) Earnings Report: Q4 2015 Conference Call Transcript. Accessed at http://www.thestreet.com/story/13445721/1/gilead-sciences-gild-earnings-report-q4-2015-conference-call-transcript.html. Accessed on 1 April 2016.
(10) Wyden-Grassley Sovaldi Investigation Finds Revenue-Driven Pricing Strategy Behind $84,000 Hepatitis Drug. Accessed at http://www.finance.senate.gov/ranking-members-news/wyden-grassley-sovaldi-investigation-finds-revenue-driven-pricing-strategy-behind-84-000-hepatitis-drug. Accessed on 18 March 2016.
(11) Taylor, P., France agrees lowest Sovaldi pricing in EU, *PMLive*, 21st November 2014. www.pmlive.com/pharma_news france_agrees_lowest_sovaldi_pricing_in_eu_618661
(12) Lavanchy, D. (2011) Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect*. 2011 Feb;17(2):107-15. doi: 10.1111/j.1469-0691.2010.03432.x. http://www.ncbi.nlm.nih.gov/pubmed/21091831
(13) Source: World Bank. http://data.worldbank.org/indicator/SH.XPD.PCAP
(14) Londeix, P. (2014). Strategies for Achieving Universal Access. http://hepcoalition.org/IMG/pdf/web_daas_strategies_for_achieving_universal_access_en.pdf. 7.

EGYPT: AN ALTERNATIVE APPROACH TO A PUBLIC HEALTH CRISIS

Egypt has a population of approximately 12 million HCV infected patients[15]. At 10% of Egypt's population, this is the highest proportion of infected people in the world.[16] Treating all of them with originator sofosbuvir at Gilead's reduced flat price of $900 per course of treatment would cost almost $11 billion, more than double Egypt's public healthcare expenditure in 2011 of $4.7 billion[17].

Thanks to local generic production of new DAAs, which has brought the price down to as little as $336[18], and a public health approach led by the Egyptian government, the situation is slowly changing. In 2015, up to 250,000 patients in Egypt were treated. The government intends to treat 1 million patients in 2016.

Voluntary licensing is one strategy used by pharmaceutical companies to make their drugs available at lower prices in LMICs. Two companies, Gilead and Bristol-Myers Squibb (BMS), have signed voluntary licensing agreements. For sofosbuvir, Gilead has signed agreements with 11 India-based generic pharmaceutical companies to manufacture and sell this drug in 101 countries.[19] Under these agreements, generic drug companies pay a royalty to Gilead on sales, but set their own prices and can receive a complete technology transfer of the Gilead manufacturing process, enabling them to scale up production as quickly as possible. Although the licensees may set their own prices, the voluntary license mechanism should bring drug prices down by bringing multiple generic companies onto the market.

However, as a wide range of civil society groups and non-governmental organizations (NGOs) have argued, a large number of patients in middle-income countries cannot access these medicines as their countries are excluded from these licenses.[20] Gilead prevents generic licensees from supplying sofosbuvir to the excluded countries except under extremely limited circumstances, where Gilead does not have a patent *or any reasonable possibility of a patent being granted.*[21] Gilead has patents granted or pending in 19 of the 38 middle-income countries not covered by the voluntary license[22], leaving a population of approximately 42 million HCV infected people[23] without access to lower-priced sofosbuvir, unless other actions are taken by governments to remove the patent barriers. Although voluntary licensing to generic manufacturers is a tool to improve affordability for people in LMICs, Gilead's approach is inadequate to cover the enormous number of patients in the middle-income countries.

Tiered pricing is another strategy that companies often say they use to make their drugs available, but as with voluntary licensing, it does not necessarily result in wide-scale affordable access. Gilead offers a single, reduced flat price for its originator sofosbuvir in the 101 countries covered by its voluntary license of $900 per course of treatment.[24]

CORPORATE INTERESTS OVERRIDE PATIENT NEEDS

One example where patient needs took a backseat is perfectly illustrated by the discontinuation of a promising regimen.

Phase II trial results of an all-oral, once-daily combination of sofosbuvir (Gilead) and daclatasvir (Bristol-Myers Squibb, BMS) demonstrated cure rates ranging from 88% to 100% after 12 or 24 weeks of treatment, regardless of genotype, treatment history, ribavirin use, or IL28B polymorphism. These promising results should have led to a larger phase III study to verify the safety and efficacy of the tested drug regimen, and to provide data that support drug registration with regulatory agencies.

Despite the exciting results, Gilead decided to discontinue further studies to avoid sharing profits from the marketed product with BMS. Instead, Gilead chose to move forward with its own in-house combination of sofosbuvir and ledipasvir. While the data of this combination on genotype 1 patients appear to be just as good, for many years patients with genotype 3 have missed out on the excellent efficacy offered by the combination of sofosbuvir and daclatasvir.

"Pharmaceutical companies are likely to prioritize a combination of their own molecules rather than collaborating with competing companies and combining the best-in-class molecules for the benefit of patients."

Michael P. Manns & Thomas von Hahn*

(15) *See* Lavanchy, D. (2011), note 12.
(16) McNeil, D. Curing Hepatitis C in an Experiment the Size of Egypt. The New York Times Online, December 15, 2015. http://www.nytimes.com/2015/12/16/health/hepatitis-c-treatment-egypt.html
(17) *See* Londeix, P. note 14
(18) *See* McNeil, D. note 16
(19) Gilead HCV Generic Agreement Fast Facts (2016). http://www.gilead.com/~/media/files/pdfs/other/hcv%20generic%20agreement%20fast%20facts%20021616.pdf. Income group classification according to the World Bank scale. http://chartsbin.com/view/2438.
(20) *See, generally,* Londeix, P.; Baker B. (2014). Gilead's hepatitis C medicines license-troubling territorial exclusions, illusory exceptions, and tiered pricing policy fracture global access. Health GAP. http://www.healthgap.org/hep_c; MSF Briefing Document, May 2015. Strategies to Secure Access to Generic Hepatitis C Medicines.
(21) *See* Baker. *See also* template of Gilead voluntary license agreement for sofosbuvir, Article 4, accessed at http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_%28FINAL%29.pdf
(22) Thompson Reuters report prepared for World Health Organization (2015). Patent Situation of Key Products for Treatment of Hepatitis C. http://www.who.int/phi/implementation/ip_trade/sofosbuvir_report_updated.pdf
(23) *See* Lavanchy, D. note 12
(24) Gilead Chronic Hepatitis C Medicines Pricing (2016).

(*) "Novel therapies for hepatitis C — one pill fits all?" *Nature Reviews Drug Discovery* 12, 595–610 (2013) doi:10.1038/nrd4050.

However, when this price is multiplied by the number of patients in each country, the total cost of treatment is exorbitant. Indonesia, for example, has a population of approximately 9 million HCV infected patients.[25] Even at $900 per patient, treating all patients would cost $8 billion for sofosbuvir alone, which was the entire public healthcare expenditure of Indonesia in 2011.[26]

Other access barriers: In addition to these pricing and intellectual property barriers, HCV patients in LMICs face practical and programmatic challenges to access care and treatment. First, largely due to the price of treatment, few LMICs have launched significant national HCV programs to increase awareness about the disease and to scale up diagnosis and treatment. Poor knowledge of HCV epidemiology leads to a lack of screening, and lack of awareness among health care workers means signs and symptoms go undetected. In addition, LMICs have large numbers of marginalized and vulnerable people with HCV, including people who inject drugs and people co-infected with HIV, for whom treatment can be more complex. There is little awareness in the general population about HCV, its impact, and its treatment.

Profit-driven R&D creates bias in research priorities

Currently, there are more than three hundreds of clinical trials related to HCV treatments. Over 80% of the studies are performed in North America, Europe, and Japan. The majority of R&D efforts are focused on genotypes that are prevalent in these high-income countries, where only an estimated 5% of those living with HCV reside. Most of the marketed DAAs so far target genotype 1, and have lower efficacy against other genotypes. Approximately 75% of Americans with HCV have genotype 1 and 20-25% have genotypes 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6. Very few genotype 4, 5, and 6 patients were enrolled in earlier trials, simply because they did not represent a significant "customer base."

Genotype 5 represents 58.8% of HCV infection in southern Africa, affecting 887,000 individuals. Genotype 6 is commonly found in South Asia and Southeast Asia. Taken together, an estimated 9.3 million patients are infected by the two genotypes in these areas. Profit-driven R&D prevents timely development of, and access to, effective treatments for patients in LMICs where genotype distribution differs from the U.S. and other wealthy markets – as shown by the abandoned Gilead and BMS collaboration described above (page 5, "Corporate interests" box).

Finding optimal treatments and making them available in a timely manner

Projections based on modeling of the U.S. population indicate that one-third of people with HCV will have cirrhosis by 2020.[27] The situation is largely similar in other regions. Timely availability of HCV treatment is of the essence to slow disease progression and reduce mortality and morbidity.

Andrew Hill from the University of Liverpool and colleagues presented the first analysis of predicted generic manufacturing costs for ribavirin and four DAAs – daclatasvir, sofosbuvir, faldaprevir, and simeprevir – based on compound properties including chemical structure, complexity of synthesis, daily dose, and minimum volumes, and then compared with the lowest prices of antiretrovirals with similar structures reported to Médecins Sans Frontières/Doctors Without Borders (MSF) by pharmaceutical manufacturers.[28]

Hill *et al.* have reported the cost analyses as follows:[29,30]

PREDICTED MINIMUM COST PER PERSON FOR 12 - 24 WEEK COURSE OF DAA

HCV DAA	Patent expiry	Class/daily dose	Total dose (12 wk)	Predicted cost (US $)
ribavirin	generic	1000 - 1200 mg	84 - 100g	$20-63
daclatasvir	2027	NS5A/60 mg	5g	$10-30
sofosbuvir	2029	NtRTI/400 mg	34g	$68-136
faldaprevir	2029	PI/120 mg	10g	$100-210
simeprevir	2026	PI/150 mg	13g	$130-270

The marketed drugs are priced a thousand times higher than the actual manufacturing costs. For example, the price for a 12-week course of sofosbuvir is $84,000. The manufacturing price is merely $68 to $136. As with the introduction and scale-up of antiretroviral therapy (ART) for HIV/AIDS over the past 15 years, new and innovative public health approaches to HCV treatment will require access to affordable DAAs that are safe, efficacious, and easy-to-use in resource-limited and high-burden settings.

(25) *See* Lavanchy, D. note 12
(26) *See* Londeix, P. note 14
(27) Davis, G. L., Alter, M. J., El–Serag, H., Poynard, T., & Jennings, L. W. (2010). Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*, 138(2), 513-521.
(28) Hill, A., Khoo, S., Simmons, B. & Ford, N. What is the minimum cost per person to cure HCV? 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur. Late breaker poster TULBPE16. Accessed on Nov 22, 2013 at http://i-base.info/htb/wp-content/uploads/2013/07/HTB-JulAug-2013e.pdf#page=22
(29) Hill, A., Khoo, S., Simmons, B., & Ford, N. (2013) Minimum costs to produce Hepatitis C Direct Acting Antivirals. Poster presentation at 64th Annual Meeting of AASLD, Washington DC, United States of America, November 2013 [Poster 1097] (http://freepdfhosting.com/d4a7e2bba6.pdf, accessed on Nov 12, 2013).
(30) Hill, A., Khoo, S., Fortunak, J., Simmons, B., & Ford, N. (2014). Minimum costs for producing Hepatitis C Direct Acting Antivirals, for use in large-scale treatment access programs in developing countries. *Clinical Infectious Diseases*, ciu012.

DND*i*'S HCV PROJECT: ENABLING A PUBLIC HEALTH APPROACH FOR HCV PATIENTS IN LOW- AND MIDDLE-INCOME COUNTRIES

DND*i*'s HCV project aims to deliver affordable combinations of DAAs that will be optimal for public health use. This project will be complementary to and synergistic with other efforts aimed at increasing access to treatment for patients and improving HCV education, surveillance, screening, testing, and linkage to care and prevention. It will accelerate the development of drug candidates already in the pipeline independent of the for-profit efforts led by the pharmaceutical industry. It focuses on the creation of a short-course, affordable, easy-to-use, highly efficacious and safe, all-oral pan-genotypic regimen that will enable countries to implement a public health approach to the HCV epidemic.

A public health approach to HCV should aim to identify and treat not only those in immediate need of therapy (those at risk of liver fibrosis and cancer) but also all those infected, in order to prevent the long-term morbidity and mortality associated with HCV, as well as reduce further transmission of the virus. Such an approach could build on lessons from efforts to scale up HIV/AIDS treatment in resource-limited settings and includes 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 expensive and sophisticated lab monitoring.

The cornerstone of a public health approach to HCV will be 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.

DND*i*'s R&D strategy aims to deliver such tools. The two main components that form the foundation of this strategy include:

(1) Accessing compounds in late-stage development through licensing;
(2) Evaluating and performing clinical development of optimal regimens of simple-to-use and affordable DAAs.

Competition to introduce new, all-oral regimens is reaching its peak and drugs currently in development are losing their commercial attractiveness due to competition, late entry, and market saturation. The smaller or slower players will have to employ out-licensing to realize value on their R&D investments.

Under these conditions, an organization such as DND*i*, which has demonstrated its ability to carry out clinical development of suitable combination regimens in other disease areas, could identify candidates available for licensing, and create optimal combination regimens through mix-and-match. The clinical development risk is reduced and timelines can be shortened by using the data already published on developed drugs from the same chemical and therapeutic classes.

A 'for-patient' pipeline can focus on collaboration rather than competition, and can pursue the end goal of affordable access as opposed to profit maximization.

Demonstrating the safety, efficacy, and ease of use of DAA regimens to enable a public health approach to the HCV epidemic

DND*i* will begin its HCV project with Phase III clinical studies in Malaysia and Thailand that will compare sofosbuvir plus the drug candidate ravidasvir with the current standard of care, sofosbuvir plus daclatasvir. These studies will be conducted in 2016 and 2017 with the close cooperation of both the Malaysian and Thai governments.

The current 5-year project consolidates DND*i*'s plans into a single strategy. DND*i*'s initial HCV strategy was comprised of a short-term R&D effort to establish, in large clinical trials in Malaysia and Thailand, the feasibility of using DAAs as public health tools. The plan was to use the well-established sofosbuvir plus daclatasvir combination. The medium-term plan was to accelerate the development of selected early clinical/late preclinical stage drugs already in the pipeline. DND*i* decided

Rosalyn, 58, is a community leader and former drug user who was diagnosed with hepatitis C over 25 years ago in Kedah, in Northwestern Malaysia. When severe symptoms of the disease began recently, she was given interferon treatment but had to stop when the side effects turned her life into "hell."

"My doctor at the University Malaya Specialist Centre (UMMC) hospital told me there is a magic drug sofosbuvir that treats hepatitis C without any side effects. I don't know if I will get that treatment because there is a long waiting list in the hospital. You need to fulfil a lot of criteria like viral load count, condition of the liver, age, etc for getting that drug. In short, only the most needy will get it," Rosalyn says.

UMMC is one of the hospitals where DND*i*'s clinical studies will take place in Malaysia.

"I love my community and I don't want people to go through the kind of stigma and discrimination I went through," she says.

to combine these short- and medium-term plans when the data from Phase III clinical trials of ravidasvir, an NS5A inhibitor drug candidate, were published in December 2015.

Ravidasvir was developed by California biotech Presidio Pharmaceuticals (Presidio). Presidio's licensing partner, the Egyptian generic manufacturer Pharco Pharmaceuticals (Pharco), performed a Phase III clinical trial with this drug in 300 patients in Egypt. When used in combination with sofosbuvir, ravidasvir showed a 100% cure rate in non-cirrhotic patients, and 94% cure rate in cirrhotic patients.[31]

Based on such promising data, DND*i* decided to include the combination of ravidasvir and sofosbuvir in its clinical trials in Malaysia and Thailand, with daclatasvir and sofosbuvir as the comparator. These studies will enroll approximately 1,000 participants and will evaluate the efficacy, safety, and pharmacokinetics of the sofosbuvir and ravidasvir combination in patients with various levels of liver fibrosis, various genotypes, and with/without HIV co-infection.

Pharco has agreed to supply DND*i* with the combination of ravidasvir and sofosbuvir for its clinical studies for $300 per course of treatment. DND*i* will also ensure an affordable, quality-assured source of generic daclatasvir for its studies.

In combination, sofosbuvir and daclatasvir have been approved by the FDA for treating genotypes 1 and 3, and individually, the drugs have been approved by the European Medicines Agency (EMA) for genotypes 1, 2, 3, and 4. Results of clinical trials had shown the high potency and safety of the sofosbuvir plus daclatasvir combination[32]. In the European Association for the Study of Liver treatment guidelines of May 2015, sofosbuvir plus daclatasvir was the only recommended pan-genotypic treatment.

If results of these studies with sofosbuvir plus ravidasvir are successful, they will show the regimen's usefulness against genotypes 1, 3, and 6. As mentioned above, data for genotype 4 is already available, so to complete the strategy DND*i* envisages, additional studies will need to be completed for genotypes 2 and 5.

Malaysia and Thailand were chosen as they both have a high prevalence of HCV, in particular genotype 3, and were excluded from voluntary licensing agreements for recently-approved DAAs. Thailand has an established HCV control program and has demonstrated resolve in taking appropriate measures to fight the HIV/AIDS epidemic. Both countries have the capacity to scale up HCV screening and linkage to care following the results of this project.

Sofosbuvir plus daclatasvir would be an acceptable public health tool, as would sofosbuvir plus ravidasvir if proven to be non-inferior to the other combination in DND*i*'s clinical studies. As assessed by Hill *et al.*[33] and by DND*i*'s own internal analysis, the manufacturing costs of the sofosbuvir and daclatasvir combination could be driven down to $166 or $200 for a 12-week course of treatment.

Equitable licensing agreements and a price of $294 or less per treatment course

In March 2016, DND*i* concluded agreements with Presidio and Pharco that secured the rights to ravidasvir, and supplies of ravidasvir and sofosbuvir, on terms that would make this combination treatment, once approved, viable as a public health tool at a price of $294 or less per treatment course. DND*i* anticipates that this price will decrease with higher sales volumes and increased competition.

Presidio has granted DND*i* a non-exclusive license to ravidasvir for LMICs (see Annex 1). In addition, it has given DND*i* an option to take non-exclusive licenses to high-income countries after a two-year period (see Annex 2). The licenses include a full complement of rights to enable DND*i* to develop ravidasvir as a treatment for HCV and to register, manufacture, distribute, and sell the treatment in the countries covered, either by itself or with a partner.

In return for the licensing rights, Presidio will receive single-digit royalties on net commercial sales of the treatments (see annexes for details). The treatments will be sold on an affordable basis, de-linking R&D costs from the price of the product, meaning that the

Rashid Bin Hashim, a former drug user, an active member of Hepatitis Support Group, Hospital Selayang, Batu caves, Selangor, Malaysia.

"The majority of hepatitis C patients in Malaysia are from the drug user community and it is difficult for them to have access to hepatitis C treatment, mainly because they don't know their status. Secondly, they don't go to hospitals to avoid facing discrimination and stigma attached with drug users."

(31) Esmat, G., El Raziky, M., Gomaa, A., Tamer, E., Abouelkhair, M.M., Sabry, A., El Deen, H.G., Ashour, M.K., Abdel-Hamid, M., Nada, O., Helmy, S., Abdel-Maguid, H., Colonno, R., Brown, N., Ruby, E., Vig, P, Imam Waked, I.. High Virologic Response Rate in Egyptian HCV-Geno- type 4 Patients Treated with Ravidasvir (PPI-668) and Sofosbuvir: Results of a Large Multicenter Phase 3 Registrational Trial. AASLD Liver Meeting. San Francisco, November 13-17, 2015. Abstract LB-4.

(32) Nelson, D. R., Cooper, J.N., Lalezari, J.P., Lawitz, E., Pockros, P.J., Gitlin, N., Freilich, B.F., Younes, Z.H., Harlan, W., Ghalib, R., Oguch,i G., Thuluvath, P.J., Ortiz-Lasanta, G., Rabinovitz, M., Bernstein, D., Bennett, M., Hawkins, T., Ravendhran, N., Sheikh, A.M., Varunok, P., Kowdley, K.V., Hennicken, D., McPhee, F., Rana, K., Hughes, E.A.; ALLY-3 Study Team. (2015) All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015 Apr;61(4):1127-35.

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

price will be based on manufacturing and distribution costs, not R&D costs, plus a small but sustainable margin.

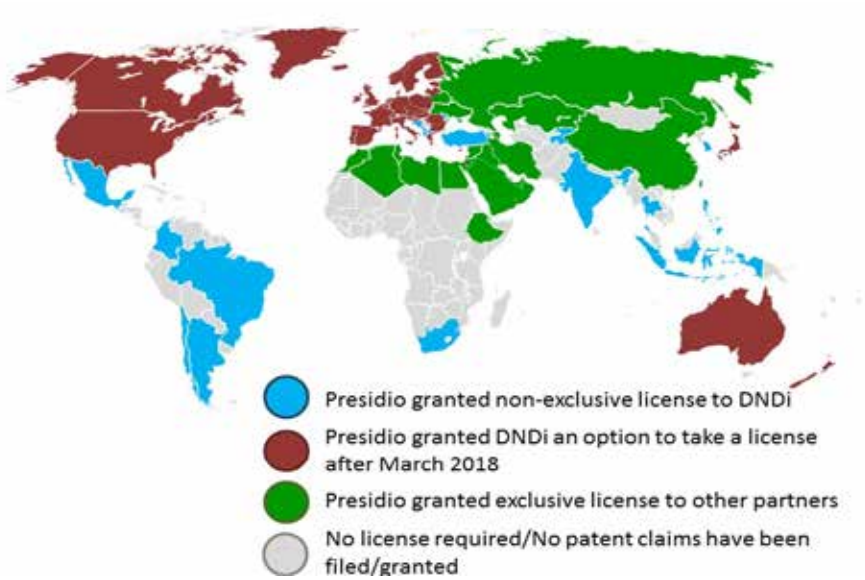
Presidio will make further efforts to promote affordable access to ravidasvir by considering offers from other interested organizations to take non-exclusive licenses, and including in any license agreement the same affordable access terms as agreed with DND*i*, meaning the single-digit royalties on net sales and affordable pricing. In addition, Presidio will consider entering into negotiations with the Medicines Patent Pool (MPP) for the granting of additional non-exclusive licenses in order to accelerate and broaden the manufacture and distribution of ravidasvir.

There are some countries not included in the DND*i* license with Presidio because the company had previously granted an exclusive license to another entity prior to the DND*i* agreement on 21 March 2016 (see Annex 3). Countries not included in Annexes 1, 2, or 3 do not require a license because patent claims have not been filed by Presidio.

Complement countries' efforts to lower intellectual property and pricing barriers

DND*i*'s R&D strategy aims to deliver safe, efficacious, affordable, and easy-to-use DAAs, and to help demonstrate the feasibility of a public health approach for treating and controlling HCV with these new, superior therapies.
If the clinical trials are successful, governments all over the world may use the experience in Malaysia and Thailand as a basis for developing their own national strategies for tackling the HCV epidemic. Although DND*i* has succeeded in obtaining favorable licensing terms for ravidasvir and sofosbuvir, in order to make DAAs widely available on an affordable basis countries also will need to use all policy tools at their disposal to overcome intellectual property and pricing barriers.
Such strategies could include price negotiations, voluntary licensing agreements, and the use of TRIPS [34] flexibilities such as patent

RAVIDASVIR LICENSING TERRITORY



PATHS TO AFFORDABLE HCV TREATMENT

For HCV drugs, there are several ways that more affordable drug prices could be achieved to allow access for individual patient care and for a broader public health benefit. The following options are notable:

- **Negotiation** with pharmaceutical companies to secure equitable access to new HCV treatments at a price that is genuinely affordable to patients and health systems, based on local economic conditions;
- **Licensing of key HCV medicines**, including under voluntary license programs that open all LMICs to generic competition, and patent sharing through organizations such as the Medicines Patent Pool (MPP). Patent sharing is an effective way of sharing innovative products in resource-poor settings. Low-cost producers and product development partnerships can make and sell affordable, adapted HCV medicines, and sales may be compensated by a fair royalty;
- **Tiered pricing**, in which the drug price is set by the manufacturers according to local economic conditions to ensure equitable access and affordability;
- **Patent opposition** - also called patent challenge, a procedure administered by the patent office of a country which allows any third party to oppose the granting of a patent on grounds that it does not meet the standards for patentability under that country's laws, for example, lack of novelty;
- **Compulsory licensing**, by which LMICs exercise their rights to allow generic producers to manufacture selected drugs that are under patent protection, and compensate the patent holders based on a set of predetermined criteria.

While these all could be options to achieve affordable access to existing drugs, a sustainable approach is needed to develop new drugs or regimens specifically for patients in LMICs that are effective, feasible, and affordable.

(34) The Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organization (WTO) sets forth minimum standards for intellectual property protection. "TRIPS flexibilities" refers to fully legal steps governments can take to overcome intellectual property barriers to access to medicines, including compulsory licensing, parallel importation, etc. and were reaffirmed in the November 2001 Declaration on the TRIPS Agreement and Public Health (Doha Declaration), available at https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm.

oppositions, refusing data exclusivity, and compulsory licensing. DND*i*'s R&D efforts aim to complement all of these strategies.

Support Affordable Access via Coordination with Stakeholder Efforts

Coordination with governments, industry, civil society/activist groups, patient networks, and other key stakeholders is necessary to procure DAAs at prices that will allow governments to afford and sustain dramatic scale-up of treatment for people with HCV. In addition to conducting "for-patient" R&D, DND*i* will engage with governments and key stakeholders to develop and support local and regional strategies for lowering barriers to access to treatment.

A powerful global HCV treatment access movement has emerged over the past several years which has established multi-pronged strategies to overcome intellectual property and pricing barriers. In recognition of this, DND*i* has created a Hepatitis C Advisory Group (HepCAG) to help guide the project and ensure that DND*i*'s efforts at supporting affordable access and those of other organizations complement one another. The HepCAG was created in October 2015 and comprises scientific experts, opinion leaders, key civil society organizations, and access to medicines experts.

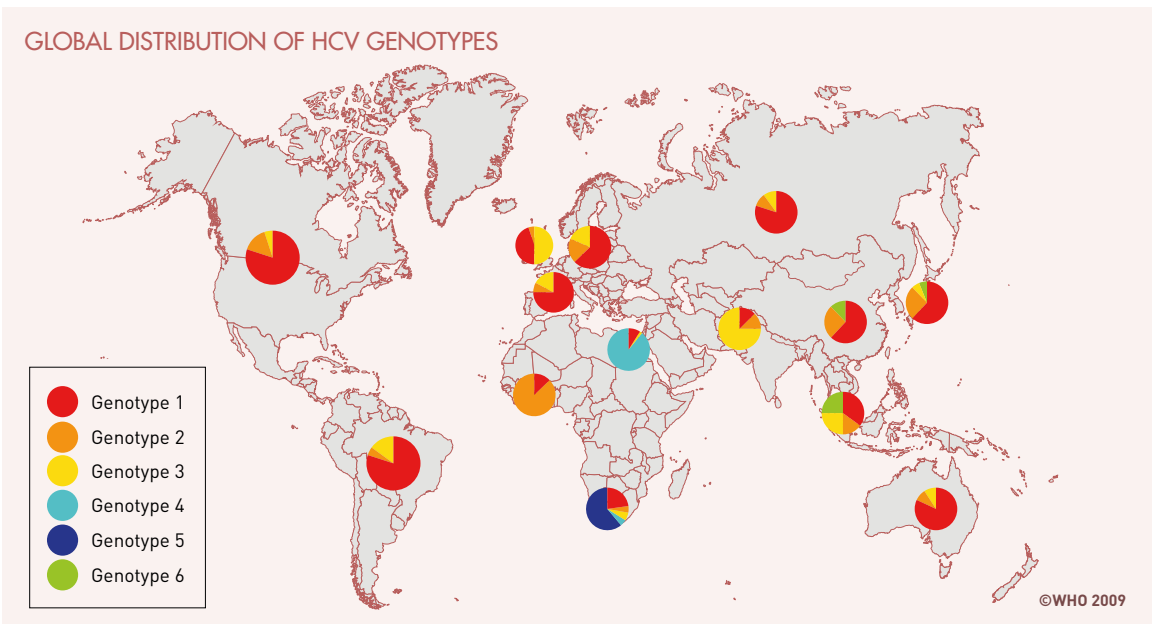
Finally, in addition to the studies in Malaysia and Thailand, DND*i* will support local and regional pilot programs in other key regions where DND*i* is active. This strategy will develop further as we continue to engage with regional and local stakeholders, with the support of the HepCAG.

CONCLUSION

The barriers keeping the vast majority of people with hepatitis C from benefitting from new therapeutic breakthrough are a result of the current biomedical R&D system. On the one hand, the needs of patients in low- and middle-income countries are largely ignored because they do not represent a sufficiently lucrative 'market' for industry and investors; on the other hand, even when useful innovations are developed, they are priced out of reach of those who stand to benefit most – because the current incentive system for R&D (intellectual property rights) grants 20-year patent monopolies, facilitating high drug prices even when they do not reflect actual R&D and manufacturing costs but rather what the market will bear in the absence of competition.

Every four to five years, DND*i* reviews the global health R&D landscape to identify new unmet R&D needs and gaps, and to determine whether the organization can help play a role in addressing these needs. In response to the urgent need for affordable, easy-to-use, pan-genotypic HCV treatments that can be used on a large-scale in public health programs, DND*i*'s Board of Directors agreed in 2015 to include HCV (among other disease areas) in its portfolio.

The project described in this document summarizes DND*i*'s efforts to support the global struggle for access to affordable HCV treatment, and to contribute in a modest way to meeting the needs of people with HCV – by bringing the best science to even the most neglected HCV patients.



ANNEXES

ANNEX 1

Countries in which Presidio has granted DND*i* a non-exclusive license to ravidasvir as of 21 March 2016

Country	Per capita income, 2013 (GNI Atlas method)	Relative to US income, in 2013	Royalty rate (% of net sales)	Estimated number HCV cases[35]
Albania	$4,510	8%	4%	1,000
Argentina	$14,220	26%	7%	77,000
Bosnia and Herzegovina	$4,790	9%	4%	58,605
Brazil	$12,310	23%	7%	1,790,000
Chile	$15,270	28%	7%	185,000
Colombia	$7,770	14%	7%	75,000
India	$1,530	3%	4%	15,000,000
Indonesia	$3,740	7%	4%	2,620,000
Kyrgyzstan	$1,220	2%	4%	205,880
Mexico	$9,770	18%	7%	906,000
Montenegro	$7,250	13%	7%	1,000
Philippines	$3,300	6%	4%	1,040,000
Republic of Korea	$25,870	48%	7%	543,000
Republic of Moldova	$2,470	5%	4%	99,498
South Africa	$7,410	14%	7%	760,000
Swaziland	$2,750	5%	4%	18,030
Tajikistan	$1,000	2%	4%	22,000
Thailand	$5,320	10%	4%	1,411,000
The former Yugoslav Republic of Macedonia	$4,980	9%	4%	40,800
The Republic of Armenia	$3,780	7%	4%	133,012
Turkey	$10,970	20%	7%	1,215,000

ANNEX 2

Countries in which DND*i* has an option to take a non-exclusive license to ravidasvir from Presidio after 21 March 2018

Country	Per capita income, 2013 (GNI Atlas method)	Relative to US income, in w013	Estimated number HCV cases[35]
Australia	$65,410	121%	449,000
Austria	$50,390	93%	17,000
Belgium	$46,340	86%	177,000
Bulgaria	$7,280	13%	112,000
Canada	$52,570	97%	301,000
Croatia	$13,470	25%	12,000
Cyprus	$27,520	51%	2,000
Czech Republic	$18,970	35%	26,000
Denmark	$61,740	114%	52,000
Estonia	$17,970	33%	6,000
Finland	$48,910	90%	11,000
France	$43,550	81%	1,088,000
Germany	$47,250	87%	1,473,000
Greece	$22,610	42%	162,000
Hungary	$13,260	25%	26,000
Iceland	$46,650	86%	1,500
Ireland	$43,080	80%	8,000
Israel	$33,930	63%	11,000
Italy	$35,430	66%	1,891,000
Japan	$46,330	86%	1,430,000
Latvia	$15,280	28%	9,000
Liechtenstein	$119,918	222%	No data available
Lithuania	$15,100	28%	14,000
Luxembourg	$69,880	129%	1,000
Monaco	n/a	n/a	No data available
Netherlands	$51,060	94%	280,000
New Zealand	$39,300	73%	10,000
Norway	$104,260	193%	9,000
Poland	$13,440	25%	536,000
Portugal	$21,310	39%	20,000
Romania	$9,050	17%	646,000
San Marino	n/a	n/a	No data available
Singapore	$54,580	101%	5,000
Slovakia	$17,810	33%	14,000
Slovenia	$23,220	43%	5,000
Spain	$29,940	55%	91,000
Sweden	$61,750	114%	22,000
Switzerland	$90,670	168%	17,000
United Kingdom	$41,590	77%	1,643,000
United States of America	$54,070	100%	3,403,000

ANNEX 3

Countries in which a license for ravidasvir is not available to DND*i*

Country	Estimated number HCV cases[35]
Azerbaijan	45,000
Belarus	226,600
Kazakhstan	474,592
Russia	3,161,000
Ukraine	197,000
Algeria	42,000
Bahrain	1,000
Djibouti	2,637
Egypt	6,023,000
Ethiopia	127,000
Gaza	No data available
Iran	1,434,000
Iraq	273,000
Jordan	25,000
Kuwait	4,000
Lebanon	7,000
Libya	7,000
Malta	4,000
Morocco	43,000
Oman	34,836
Qatar	1,000
Saudi Arabia	254,000
Syria	310,000
Tunisia	16,000
United Arab Emirates	6,000
West Bank	No data available
Yemen	412,352
Hong Kong SAR	No data available
Macau SAR	No data available
People's Republic of China	17,425,000
Taiwan	No data available

(35) Global distribution and prevalence of hepatitis C virus genotypes. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. *Hepatology*. 2015 Jan;61(1):77-87. doi: 10.1002/hep.27259. Epub 2014 Jul 28. Supplementary info available at http://onlinelibrary.wiley.com/store/10.1002/hep.27259/asset/supinfo/hep27259-sup-0001-suppinfo.pdf?v=1&s=39a05a66c7c4d5f1f806b467fe1e66cd61cce272 When info was not available at Messina *et al.*, an alternative source has been used: Evolving epidemiology of hepatitis C virus. Lavanchy D. *Clin Microbiol Infect*. 2011 Feb;17(2):107-15. doi: 10.1111/j.1469-0691.2010.03432.x.

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