Inflammatory liver disease caused by the hepatitis C virus (HCV) is transmitted through exchange of body fluids, mostly through exposure to contaminated blood.

- 55-85% of patients develop chronic infection; of those, 15-30% are at risk of cirrhosis of the liver within 20 years.
- The virus exists as six major genotypes (GTs); prevalence varies by region with GT1 most prevalent in high-income countries and GT3 in low- and middle-income countries.
- Current treatments are effective, but few patients have access to diagnosis and treatment, notably due to exorbitant prices.

Direct-acting antivirals have revolutionized the therapeutic landscape. With cure rates of 95%, these 12-week oral treatments have replaced less effective, injection-based 48-week regimens associated with side effects. But their price is a major barrier to access, with treatment reserved for the most severe cases, and middle-income countries often excluded from price discounts.

The development of an affordable pan-genotypic regimen that works for all patients, including the most vulnerable, combined with innovative models of care that allow test-and-cure strategies, would set the foundations for a public health approach to the HCV epidemic to be implemented.

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 with the current price tag."

DNDi aims to deliver:

- A safe, effective, and easy-to-use direct-acting antiviral regimen, to be used as an affordable combination paving the way for a public health approach to HCV.
Ravidasvir/sofosbuvir

**OBJECTIVE:** Conduct Phase II/III clinical trials to test the efficacy of a combination of sofosbuvir + ravidasvir

**Background:** More than one million people in Thailand, and 400,000 in Malaysia are estimated to be infected with chronic HCV. The most prevalent genotypes are 1, 3, and 6. Yet, both countries are excluded from global voluntary licensing agreements that enable access to generic HCV treatments.

A Phase II/III study started in Malaysia and Thailand aims to assess, in real-world settings, the efficacy, safety, tolerability, pharmacokinetics, and acceptability of a 12-week regimen containing sofosbuvir in combination with the drug candidate ravidasvir, supplied by Egyptian manufacturer Pharco. Participants are included regardless of genotype, source of transmission (including intravenous drug use), or HIV co-infection. Patients with compensated liver disease with or without cirrhosis, will also be included (for participants with compensated liver cirrhosis, treatment duration will be 24 weeks). A total of 750 patients will be enrolled, including up to 30% with compensated cirrhosis and up to 20% who inject drugs, providing data on efficacy and safety of the combination, as well as on treatment compliance.

At the end of 2016, six study sites in Malaysia had recruited 164 patients (out of a target of 300) and four sites in Thailand had been initiated, with the full cooperation of the Ministries of Health in these countries. Sites in additional countries including Vietnam should be initiated in the coming months.

We hope that Pharco’s collaboration with DNDi to develop a combination treatment that costs $3.50 per day or less — as opposed to $1,000 per day for only one pill — will save millions of lives, and lead to widespread access to safe, effective and affordable treatment for hepatitis C patients around the world.

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164 patients recruited at 6 sites

Innovative licencing agreement to ensure affordable access.

Ravidasvir licencing territory

- Non-exclusive licence granted to DNDi
- DNDi has an option to take a licence after March 2018
- Exclusive licence granted to other partners
- No licence required/no patent claims have been filed/granted

Dr Sherine Helmy
CEO, Pharco Pharmaceuticals, Egypt
The powerful generation of new direct-acting antivirals (DAAs) to treat HCV have become the poster child for the prohibitive price of medicines in many countries.

New treatment regimens combining DAAs cost upwards of USD 100,000 in the US, and EUR 40,000 in European countries. Pricing of HCV drugs has led to treatment rationing in Europe and the US, where countless headlines have lamented a situation where “only the sickest receive treatment.” Politicians, activists, and patients are angry. Gilead’s USD 84,000 price tag for sofosbuvir in the US even triggered a Congressional investigation.

Pharmaceutical companies have offered DAAs at vastly reduced prices for low-income countries, with voluntary licensing deals allowing generic production. But 73% of the world’s chronic HCV patients live in middle-income countries. Most of these countries – from Brazil to Malaysia – are excluded by licensing deals. Sofosbuvir in Brazil costs anywhere from USD 5000 to USD 10,000 per patient – simply too high for the country.

The result: More people are getting infected than being put on treatment. There were 1.75 million new HCV infections globally in 2015 but only 1.1 million people started treatment. With no animal reservoir of HCV and drugs that are almost 100% effective, elimination of this viral disease is a real possibility – if we first eliminate the many barriers to access around the world.

Many activists have turned to the courts, employing the same tactics used to reduce the prices of HIV drugs in the 2000s. Patent oppositions are one option, where a third party can oppose the granting of a patent on grounds that it does not meet patentability standards. In 2015, India’s patent office rejected Gilead’s patent on sofosbuvir after activists argued that it represented only minor changes to a previous formulation. But the decision was overturned in 2016. Patent oppositions have been filed in other countries, including France and Ukraine.

Latin America is a battleground in this access showdown. A sofosbuvir patent was recently rejected in Brazil, while civil society groups in Argentina have filed an opposition to a patent request for sofosbuvir. Meanwhile the patent has been granted for sofosbuvir in other Latin American countries like Colombia, Chile, and Mexico. The Strategic Fund of the Pan American Health Organization (PAHO) will play a key role in obtaining treatments in these countries at affordable prices.

Others countries are leading by example. Egypt has approximately 12 million HCV infected patients, but thanks to local generic production of new DAAs and a public health approach, one million people have been treated. The Indian state of Punjab launched a comprehensive HCV test-and-treat programme for its 28 million inhabitants that could also be an excellent model.

DNDi’s R&D approach is synergistic with all these efforts. In conjunction with Egyptian manufacturer Pharco we are seeking to develop an affordable regimen of ravidasvir/sofosbuvir, with a target price of USD 300-500 a treatment course. Critically, the combination is intended to treat all HCV genotypes.

Our comprehensive strategy incorporates HCV education, surveillance, screening, testing, and links to care and prevention. It is also country-driven, with the ministries of health in Malaysia and Thailand co-sponsoring DNDi’s trial and providing public leadership.