

A public health approach to the hepatitis C epidemic

Extending the DAA treatment revolution to neglected patients

The context: more than four years after their introduction, access to new treatments remains highly restricted

An estimated 71 million people worldwide were chronically infected with hepatitis C virus (HCV) in 2015, 81% of whom live in low- and middle-income countries. 1.75 million new infections occurred, yet only 1.1 million people started treatment. 400,000 deaths from HCV-related liver diseases were reported over the same year. The World Health Organization's Global Strategy on Viral Hepatitis, 2016-2021 aims to test 90% and treat 80% of people with HCV by 2030. We are today very far from achieving this target.

Treatment of chronic hepatitis C has evolved rapidly and several combinations of highly effective direct-acting antivirals (DAAs) have been approved since 2013. With cure rates of 95% and above, these 12-week oral treatments have replaced less effective, injection-based 48-week regimens associated with severe and debilitating side effects.

But few patients have access to diagnosis and treatment, notably due to expensive prices of DAAs, upheld by patent monopolies that prevent access to more affordable generic medicines. Even high-income countries are affected, with the UK, for example, paying around US\$51,000 per treatment course (sofosbuvir/velpatasvir). While some DAA patent-holders have developed voluntary licensing schemes, with a view to offering more affordable prices to developing countries, too many middle-income countries are excluded, and as a result are left paying high prices, such as \$12,000 in Chile (sofosbuvir/ledipasvir), or \$6,212 in Brazil (sofosbuvir/daclatasvir).

Most government treatment programmes are thus forced to restrict HCV treatment to the most critically ill patients, those who have advanced liver disease. This form of treatment rationing means excluding millions of neglected patients from the DAA revolution.

Beyond the fact that patients are forced to postpone treatment, at current treatment rates we are failing to keep up with transmission rates, and we are no closer to pushing back the disease. Yet because HCV can be cured, if people are diagnosed and treated sufficiently early enough to avoid infecting others, the disease could be eliminated and the WHO goals could be met.

Failing to expand access to DAAs thus means failing to seize their vital potential impact for public health.

“Prices need to go down. With the savings realised, mass diagnostic campaigns would be possible, as would treating people with the early stages of the disease. Projections show that universal cure and eradication of the disease would be possible in Brazil if the patent [on sofosbuvir] is rejected and affordable generic drugs are used.”

Arair Azambuja, president of the Brazilian Movement for the Fight against Viral Hepatitis (MBHV), member of the Brazilian Social Forum to Fight Against Neglected & Infectious Diseases (FSBEIN).



The DNDi strategy: partnerships to accelerate R&D, catalyse access and simplify treatment strategies

The cornerstone of a public health approach to HCV will be ensuring the availability, accessibility and affordability of an all-oral, easy-to-use, efficacious, and safe treatment that will, to the greatest extent possible, enable the same regimen or regimens to be used for all patients, regardless of genotype, liver disease stage, HIV co-infection, or source of infection.

DNDi's HCV programme is partnering with access-oriented pharmaceutical companies, middle-income countries and other treatment providers to implement a strategy based on three mutually reinforcing pillars – first, accelerating the delivery of such a treatment, through the development of promising drug candidates in the pipeline; second, supporting policy change and political will to increase access to affordable treatment, for example by overcoming intellectual property (IP) and regulatory barriers; and third, working with health providers to develop simpler and innovative models of care, needed to support scale up of treatment to the millions still waiting.

1- R&D: Accelerating the development of promising drug candidates, with pharmaceutical companies and governments

The first step of DNDi's HCV programme was to conduct a pipeline analysis to assess promising compounds in late-stage clinical development that could be suitable tools for a public health approach to HCV: affordable, and with potential to be pangenotypic. Until today, the lack of sufficient competition between affordable, easy-to-use, all-oral pan-genotypic regimens that can enable a public health approach has stymied efforts to introduce and expand access to HCV treatment.

A treatment that could be administered regardless of genotype would remove expensive testing and pave the way for a simplified model of care, which will prove essential for scaling up

treatment. With an affordable treatment, public health agencies would be able to treat not only those in immediate need of therapy (those at risk of liver fibrosis and cancer) but all patients who can benefit, regardless of liver disease stage.

The DNDi pipeline analysis identified ravidasvir (RDV), an NS5A inhibitor drug candidate developed by California biotech Presidio Pharmaceuticals. Data published in December 2015 from Phase III clinical trials in Egypt by generic manufacturer Pharco Pharmaceuticals (Pharco) notably showed a 100% cure rate for the sofosbuvir/ravidasvir (SOF/RDV) combination in genotype 4 non-cirrhotic patients (170 patients), and a 94% cure rate in genotype 4 cirrhotic patients (130 patients).

DNDi then negotiated a licence to RDV, with a view to accelerating its development as part of a simple-to-use and affordable DAA regimen. In March 2016, DNDi concluded an agreement with Presidio that secured the licence rights to RDV for low- and middle-income countries, and also an agreement with Pharco to secure clinical supplies of RDV and generic sofosbuvir for the purpose of evaluating the pharmacokinetics, safety, efficacy of the combination of the two drugs in additional HCV genotypes.

The clinical trials began in Malaysia in 2016 (co-sponsored by the Ministry of Health) and in Thailand in 2017, in partnership with the government. The countries were selected as ideal partners given their high prevalence of HCV, their established HCV control programmes and capacity to scale up screening, their exclusion from voluntary licence agreements for recently-approved DAAs, and their strong public health programmes that make treatments available and affordable for their populations.

300 patients have been recruited in the trial with various levels of liver fibrosis, various genotypes, both with and without HIV co-infection. Initial results are expected in the first quarter of 2018.

If successful, these results will show the regimen's usefulness against genotypes 1, 2, 3, and 6, with data for genotype 4 already available from the earlier Egyptian study. To establish further the pan-genotypic profile of ravidasvir, these studies will be complemented by other trials

in South Africa (for genotype 5) and Ukraine (for vulnerable patient groups including injecting drug users). Registration of RDV will be pursued in Malaysia and in other middle-income countries, including in Latin America, as well as through WHO Prequalification, which will enable extension to other countries.

2- Access: Securing affordable pricing, with companies, governments and civil society

In 2016, DNDi and Pharco also concluded a collaboration agreement on access to affordable DAAs, including RDV and generic sofosbuvir. In Malaysia, Pharco has committed to make available the SOF/RDV combination, once approved, at a price of \$300 or less per treatment course for the national treatment programme. Such price represents more than a 10-fold drop compared to the cost of the existing originator DAA regimen in Malaysia. In Latin America, DNDi is negotiating with regional manufacturers to ensure local supply that would enable scale up, and Pharco has committed to partner with local manufacturers, to make the combination available at an affordable price of less than \$500 that will enable a public health approach to treating HCV. Once RDV is registered and launched in multiple countries, it is expected that the increased sales volumes will bring prices down further.

The potential geographic reach of ravidasvir as an affordable pangenotypic DAA is extensive. The non-exclusive licence granted by Presidio to DNDi, together with a non-exclusive licence signed by Pharco with the Medicines Patent Pool, extend the potential benefits to countries where 85% of people with HCV live. A successful SOF/RDV combination could thus help drive down prices in numerous countries, even in places where generic DAAs are already available; to date, competition between different manufacturers of DAAs remains limited, except for in a handful of countries. Countries most likely to benefit from a SOF/RDV combination are those excluded from pharmaceutical company voluntary licences and countries in which generic competition is not sufficiently robust to bring prices down.

Sofosbuvir, the current backbone of DAA treatments, has been the poster child of exorbitant pricing and the crisis in access to medicines since its initial pricing by Gilead at \$84,000 per treatment course in the US, or \$1000 per single pill. Where the drug is largely inaccessible because of patenting and high pricing, seizing the public health opportunity offered by DAAs and expanding treatment widely will thus require governments to take active steps to increase access and affordability, including by making use of flexibilities allowed under international trade law to overcome pricing and patent barriers.



In 2016, DNDi and the Ministry of Health of the Government of Malaysia agreed to work together to develop a public health approach to Hepatitis C within the framework of the future National Strategic Plan on viral hepatitis. In September 2017, following considerable strategic investment in the clinical trials co-sponsored by DNDi and the Ministry of Health to assess the safety, effectiveness and pan-genotypicity of SOF/RDV, Malaysia issued a government-use licence to source generic sofosbuvir, in order to accelerate access to affordable sofosbuvir in its public hospitals.

Looking ahead, the DNDi HCV programme will seek to work with governments, civil society organisations, patient networks and other stakeholders in key countries to overcome IP, regulatory, pricing and other barriers to an affordable pan-genotypic treatment, particularly too many MICs are excluded from voluntary licence schemes. In parallel, DNDi will continue to explore the pipeline of HCV drugs in development to identify an equivalent of sofosbuvir that could be developed and distributed under more favourable terms.

3- Treatment strategies: Developing innovative models of care to support scale-up, with other treatment providers

HCV is currently managed as a complex disease, difficult and expensive to diagnose and to treat, and that can only be managed by specialists in central hospitals with sophisticated screening, diagnostic, and monitoring capabilities. Together with the restrictions that ration treatment eligibility to the sickest, the absence of simplified models of care has limited the introduction and particularly the scale-up of treatment programmes.

A major part of simplifying the model of care for HCV lies in providing a pan-genotypic treatment regimen. Above and beyond that central concern, it is essential to build on the lessons learnt from the scale up of HIV treatment in resource-limited settings. Efforts are needed to accelerate decentralisation from central hospitals to the primary healthcare level and to peripheral health centres, to develop task-shifting which would reduce reliance on doctors and other highly qualified medical personnel, to reduce dependence on genotyping and other expensive and sophisticated lab monitoring, and to boost community involvement to support uptake and acceptance. With a treatment regimen that will cost \$300, Malaysia is, for example, considering strategies to decentralise treatment at the primary health care level.

DNDi's HCV programme will work with Médecins Sans Frontières (Doctors Without Borders) in the development and implementation of simpler models of care in specific target populations as well as in large-scale treatment cohorts in Cambodia and Ukraine. These efforts will include evaluating simplified testing algorithms; shorter and pan-genotypic treatment regimens; management of treatment follow up; and how to address treatment failure, interruption and resistance. The objective of these studies will be to demonstrate that the move from small-scale pilots to larger scale programmes is possible and that the challenges of scaling up can be overcome.

“As a clinician, it breaks my heart when I cannot offer my patients such good treatment just because of its exorbitant cost. You should see the shock on their faces when I tell them the price of DAAs.”

Dr SS Tan, Ministry of Health, Malaysia.

Conclusions

Seizing the public health potential of DAAs will require the development of new approaches and new models to develop simpler, pan-genotypic treatment tools. Strong leadership from Ministries of Health and governments will be needed to implement pro-access policies and affordability of new treatments. The active involvement of treatment providers and patient groups will be necessary to enable the emergence of a test and cure approach that can be scaled up to all people in need.

The journey is far from over. Only a collaborative effort bridging science and policy and uniting multiple public health stakeholders will succeed in ensuring no patients are left behind.

A not-for-profit research and development organization, DNDi works to deliver new treatments for neglected diseases, in particular leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, mycetoma, paediatric HIV, and hepatitis C. More info at www.dndi.org

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