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Closing in on a cure

Finite courses of treatment could get the hepatitis B virus under control — with the right combination of drugs. **By Elie Dolgin**

For Thomas Tu, eliminating hepatitis B is a deeply personal goal.

Tu, a molecular virologist at the Westmead Institute for Medical Research in Sydney, Australia, learnt he had chronic hepatitis B as a teenager. A blood test revealed telltale signs of the infectious liver disease, which Tu had probably acquired at birth.

In his late 20s, Tu started taking a medication to limit the virus's replication and prevent collateral damage to his liver cells. Now 36, he has been on that daily treatment — a pill known as a nucleoside analogue — ever since.

Yet, even with a therapy that keeps his infection well under control, Tu remains at heightened risk for liver disease. He must juggle visits to specialist doctors and bear prescription-drug costs. And he knows that many others — racked by the financial instability, emotional toil and stigma that the lifelong infection can bring — have it much worse.

"I'm in this quite privileged space to be able to be on therapy and not have any side effects or feel any burden from taking daily medicines," Tu says. "That's not the same for the majority of people living with hepatitis B."

That's why Tu and many other leading virologists and hepatologists continue to strive for something better: a curative fix for hepatitis B virus (HBV) infections. "Finite treatment is the aim," says Seng Gee Lim, an HBV specialist at the National University of Singapore's Yong Yoo Lin School of Medicine. "Patients don't want to be taking drugs for the rest of their lives."

According to the latest estimates[1], only around 10% of the 300 million people who carry HBV have been diagnosed. Nearly 100 million people have such advanced disease that they would probably benefit from anti-HBV drugs, yet fewer than 5 million actually take them. No wonder, then, that the virus continues to cause up to one million deaths around the world each year, mostly from liver cancer and cirrhosis linked to the infection.

Eliminating HBV infections will not be easy. Although some individuals, after years or decades of antiviral therapy, manage to suppress viral replication and can safely stop taking daily medications, such cases are rare. And even in these people, HBV is almost never eradicated: hints of viral DNA persist inside some liver cells,

although the immune system keeps the virus on a tight leash. Unless they later take some kind of immunosuppressive therapy – for cancer treatment, say, or an organ transplant – the infection is usually held in check.

Achieving that outcome in many more individuals is ultimately the goal of the HBV research community, which hopes to therapeutically quash viral activity so that the immune system, either naturally or with drug-mediated assistance, can handle any residual HBV on its own – even after treatment is halted. It might not be a complete cure, but most scientists think it's good enough.

Drug strategies under consideration take aim at nearly every stage of the HBV life cycle. There are experimental treatments designed to block viral entry into the cell, and others that should prevent the release of viral proteins from infected cells. There are drug candidates directed at viral-particle assembly and replication, and others geared at gumming up expression of viral-protein-encoding genes. Immune-activating agents are in the works, too.

"We are using all our weapons to tackle every single step of the virus," says Man Fung Yuen, a hepatologist at the University of Hong Kong.

No one has pharmacologically induced this level of viral control with any predictability. But thanks to scientific advances over the past decade, it could be only a matter of finding the right combinations of experimental drugs now in clinical testing, says Stephen Locarnini, a medical virologist at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia. "We're very close," he says. "We might very well see that final goal of functional cure being achieved in the next few years."

'The right moment'

The push to cure hepatitis B started in earnest around 2014. That's when Fabien Zoulim and other leading HBV scientists began convening scientific workshops centred on developing a cure-focused action plan.

Two years prior, researchers from China's National Institute of Biological Sciences in Beijing had discovered the receptor through which HBV enters human cells[2], allowing for the creation of new cell lines and mouse models that could be used to study viral replication and discover new drugs. And pharmaceutical companies were bringing curative therapies to market for another liver-infecting pathogen, the hepatitis C virus. Propelled by strong scientific and financial tailwinds, the drug industry was looking for a similar viral threat to go after next.

"It was the right moment to do something more," says Zoulim, a hepatologist and molecular virologist at the University of Lyon, France.

In early 2016, together with Locarnini and two colleagues, Zoulim put out a call to arms, imploring HBV researchers around the world to unite around this common objective[3]. Key stakeholders came together to devise a strategic agenda[4] – and, later that year, the International Coalition to Eliminate HBV (ICE-HBV) was born.

Less than six years on, scientists are well on the way down a path to a cure. Almost 50 therapies are now in clinical trials, and many more will soon follow.

Some scientists feel that mixtures of direct-acting antiviral drugs (which target aspects of HBV gene expression and replication) could do the trick. Others are betting on immune modulators (which enhance host antiviral defences). Most, like Peter Revill, suspect that an amalgam of both approaches will be necessary to knock out HBV. "We're going to need a combination of the virological and the immunological," says Revill, a molecular virologist at the Peter Doherty Institute and an architect of ICE-HBV.

ICE-HBV convened a symposium in September 2021 to explore which drug combinations have mechanisms that make the most sense as cures for hepatitis B. At the event, academics and industry executives discussed many competing theories – including what molecular virologist Stephan Urban at Heidelberg University Hospital in Germany describes as "observations that hint at the possibility" of achieving a cure. But as immunologist Gregory Fanning points out: "It's all about clinical data now."

"We can hypothesize forever," says Fanning, an industry consultant based in Charre, France, who previously worked on HBV drug development at Janssen Pharmaceuticals, headquartered in Beerse, Belgium. "But in the end, you have to see what's happening in the clinic."

New targets

Most of the proposed combinations for HBV elimination build off a backbone of nucleoside-analogue therapies. The standard of care for hepatitis B for nearly 25 years, these drugs behave like sand in the gears of viral replication whenever HBV attempts to make infectious particles.

To the virus's polymerase enzyme, nucleoside analogues look like any other genetic building block, ready to be incorporated into DNA as required to copy the virus – but they're not. Once the imposter molecule gets into a growing strand of viral DNA, replication grinds to a halt, and viral growth is markedly blunted.

Still, the agents rarely shut down polymerase activity entirely. So it seemed logical for drug developers to target another step in the replication process. Many companies took aim at the mechanism by which the virus packages an intermediate form of its genome inside a protein shell called a capsid. At least ten pharmaceutical firms now have some kind of capsid assembly modulator (CAM) in human trials.

In combination with nucleoside analogues, capsid-directed therapies "should be able to over time wipe out the infection", says Adam Zlotnick, a structural virologist at the Indiana University Bloomington.

That's the idea, at least. But, on the basis of early trial data, Zlotnick says, this is not happening.

Zlotnick is a scientific co-founder of Assembly Biosciences, a company based in South San Francisco, California, that is focused on developing CAMs. The company evaluated its lead clinical candidate, vebicorvir, in a year-long study – one of the longest to date involving a new anti-HBV agent. The drug, in combination with a nucleoside analogue, initially helped patients to achieve dramatic declines in genetic markers of infection. Yet, when trial participants stopped taking the therapy, levels of viral DNA quickly shot back up.

"We might very well see that final goal of functional cure in the next few years."

Zlotnick suspects that vebicorvir was not potent enough to fully prevent virus production. He hopes that next-generation CAMs now in early clinical testing might do better. Still, results from the vebicorvir trial have forced him and others to rethink their approach. Antiviral drugs directed at a few crucial proteins might have been able to wipe out hepatitis C. But HBV is a different beast, says John Tavis, a molecular virologist at Saint Louis University School of Medicine in Missouri and the incoming chair of ICE-HBV.

"They're about the same as a peach and a toaster: both are found in a kitchen," Tavis says, "but that's about it." In his view, other therapeutic strategies could be needed to get at the root cause of chronic HBV infections: a special chromosome-like structure known as covalently closed circular DNA, or cccDNA.

These tiny twists of viral DNA – often called minichromosomes – linger in the nucleus of an infected cell, where they pump out the genetic recipes for new infectious viruses. Several research teams have used gene-editing tools, such as CRISPR, to precisely target the cccDNA reservoir in mice[5], and a few biotechnology companies have expressed interest in the strategy.

But gene-editing technologies are still in their infancy, and fears of causing unwanted mutations in other parts of the genome put

many people off this approach – especially for hepatitis B, which can already be managed with nucleoside analogue therapy. Gene fixes for viral infections could yet enter clinical testing. But for now, says gene-therapy researcher Kristie Bloom at the University of Witwatersrand in Johannesburg, South Africa, "there's a lot of hesitancy".

Running interference

Companies have tried, with limited success, to find small-molecule drugs that directly target the host factors responsible for cccDNA stability or biosynthesis. "I think it is possible," says Phil Pang, chief medical officer of Vir Biotechnology in San Francisco. But as yet, no such compounds have advanced past laboratory testing.

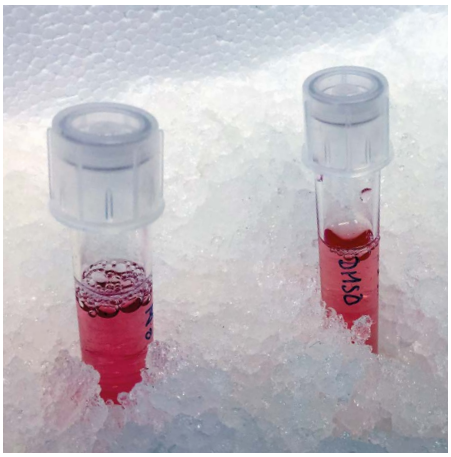
Instead, many companies, including Vir, have focused on silencing the activity of cccDNA by using drugs that cut the minichromosomes' corresponding RNA instead of targeting the special DNA structure itself. Without these RNA transcripts, no encoded proteins are made, and the immune system becomes less inured to – and thus more responsive to – the threat of the virus.

These RNA-blocking strategies, which include both antisense therapies and small interfering RNA molecules, have produced dramatic results, often driving down indicators of HBV infection quickly and durably. Last year, for example, Yuen and his colleagues reported that many individuals treated with one such RNA-targeted agent, known as bepirovirsen, saw levels of a key hepatitis B protein in the blood fall more than 1,000-fold within a month of starting the therapy[6].

Levels of this marker generally bounced back over the next six months, however, indicating that the drug doesn't achieve the functional cure researchers are looking for. Still, most scientists agree that these types of RNA-directed therapy offer a key plank in the eradication endgame.

The idea now, as hepatologist Harry Janssen at the Toronto Centre for Liver Disease in Canada explains, is to "hit the virus fast and hit the virus hard" with this type of gene-silencing therapy – "and then come in with an immune-modifying agent" to finish the job off.

The immune system probably needs therapeutic assistance because the body doesn't naturally produce many HBV-fighting T cells to begin with, says Ulrike Protzer, a virologist at the Technical University of Munich in Germany. With other viral infections – HIV, say, or cytomegalovirus (a common cause of birth defects) – more than 1% of the immune system's T-cell memory is dedicated to tackling that particular pathogen. In the case of chronic hepatitis B, she points out, the equivalent measure is closer to 0.1%.



Immune cells from people with HBV.

MARIE-LAURE PLISSONNIER

To bolster the number of HBV-directed T cells, researchers are working on several immune-stimulating strategies, the most popular being therapeutic vaccination. This involves giving people two or three shots of purified HBV proteins or harmless viruses engineered to express bits of HBV material that help to train the immune system to recognize and destroy infected cells in the liver.

"That helps to focus the response on the right antigens," says Mala Maini, a viral immunologist at University College London. "But then it may need to be combined with some other approaches," she adds, such as checkpoint-blocking molecules, common in cancer treatment, that help to lift the brakes on T-cell activity.

Some companies are incorporating drugs designed to stimulate T-cell recognition of the virus or innate immune defences in other ways. Vir, for example, has engineered an antibody therapy that can mop up HBV particles from circulation and trigger immune responses against the virus. That drug is now being tested in combination with the company's small interfering RNA agent. "You need to not just remove the stop sign on the immune system – you need to step on the gas," Pang says.

Burden of proof

That's the idea, at least. But as John Young, global head of infectious diseases at Roche in Basel, Switzerland, points out, "We don't really know what will be the right combination of agents to cure this disease. I think there's good scientific rationale associated with everything that is being tested today – by ourselves and by others – but ultimately the proof will be in the pudding."

Success might be achieved incrementally. Eradication of every last drop of HBV – both cccDNA and integrated DNA – from the liver might be unattainable. Most researchers are therefore striving towards functional cures, defined as a sustained absence of HBV proteins and genetic material from the bloodstream for at least six months after treatment ends.

"If we can get there with up to two years of treatment in 30% of patients, that's a major advance," says Anna Suk-Fong Lok, a hepatologist at the University of Michigan in Ann Arbor. The field could then build on initial successes to achieve functional cures in more people, to shorten the duration of therapy or to personalize drug regimens for better outcomes. But Lok suspects that, unlike those with hepatitis C, some people with persistent HBV infections might never be curable. "I do not anticipate that we'll ever get to the 90%-plus range," she says.

Science and drug development are not the only challenges standing in the way of HBV abolition. With such dismally low rates of diagnosis and treatment today, even if a cure were available tomorrow, "we still wouldn't make a dent" in stamping out HBV, says Tu.

People like him – who know they carry HBV and who have access to medications – might seek out curative treatment. And it's possible that the availability of an effective drug regimen could have knock-on effects throughout the entire HBV-management landscape, notes Young: "By bringing better treatment options, that will encourage more patients to get tested and seek therapy."

But that will require raising awareness, a task Tu has already taken on. Last year, he created an online support group (hepbcommunity.org), where he and other HBV scholars aim to provide trustworthy, accurate information for affected individuals. He has been outspoken at meetings and in the academic literature[7] about the need to incorporate patient perspectives in the larger research effort towards a cure to ensure the maximum impact of any future discoveries.

As the clinical enterprise continues, Tu argues that more attention must be paid to the structural challenges and inequities in health-care delivery for those with HBV. "We should be addressing them now," he says, "so that, when a cure comes, we can get people into treatment straight away."

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