The US Food and Drug Administration’s approval of two new medications for hepatitis C in May marked the dawn of an era in treating this insidious disease. The hepatitis C virus (HCV) can lurk silently for decades. Indeed, most of those who will benefit from this advance have no idea about their improved prospects, because they are unaware they are infected. The coming years could bring a surge in cases of the chronic form in people who unwittingly contracted the virus back in the 1960s and 70s through sharing needles and blood transfusions. Many of these chronic infections will progress to cirrhosis of the liver, and some to liver cancer and liver failure. Hepatitis C is the leading reason for liver transplantations. Until now, the only treatment option has been a gruelling year-long regimen of interferon-α plus ribavirin. Cruelly, in people with a particular genetic make-up, even this nasty course of medication often doesn’t work.

The newly approved antiviral drugs lead the way for many other therapies (page S5). But caution is in order. First, the new medications supplement—not replace—the current treatment. So patients will be subject to all the same side effects as before, plus possibly a few more. Moreover, as clinician and HCV activist Diana Sylvestre points out on page S11, there is a high risk that the virus will become resistant to the new drugs. Finally, on page S18 epidemiologist Brian Edlin argues US policy makers need to wake up to the lurking HCV threat, and take action. Meanwhile, Egypt is experiencing an HCV epidemic of greater intensity than that in the United States and Europe (page S12), exacerbated by the fact that the genotype of HCV in Egypt is rarely found elsewhere.

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Herb Brody
Supplements Editor, Nature Outlook.
A smouldering public-health crisis

Long overshadowed by HIV, the hepatitis C virus is starting to take its toll. And the heat is on to find and treat those affected.

BY LAUREN GRAVITZ

In the early 1980s, when AIDS was still unexplained and HIV was spreading unchecked, another blood-borne virus was also on the move. Like HIV, this unknown infectious agent struck intravenous drug users and blood transfusion recipients. But it was stealthier than HIV, often causing its victims no discomfort as it multiplied and worked up to a fully fledged attack on the liver, where it could cause cirrhosis or cancer.

That culprit, identified in 1989, was hepatitis C virus (HCV). Some 130–200 million people are now estimated to be infected worldwide. Rates of transmission in the United States, Europe and Japan have plummeted since the virus was identified, however, thanks to disposable medical instruments and a screened blood supply. But the virus continues to thrive in developing nations, which lack the resources to treat people who do not appear ill. Treatment is expensive, lengthy and causes numerous side effects — and, for all that, it works only about half the time. The upshot is that more than 350,000 people worldwide die from HCV-related liver disease every year.

Hepatitis C is just as deadly as HIV — both kill about 10,000–15,000 people per year in the United States, according to David Thomas, an infectious diseases specialist at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. But HIV gets about 30 times more research funding in the United States than HCV, he says. And as increasing numbers of chronic hepatitis C cases manifest their most serious symptoms, the smouldering problem is turning into a burning public-health issue that threatens to stretch healthcare systems to their limits.

THE QUIET EPIDEMIC

Two other viruses that target the liver were discovered before HCV: hepatitis A, which causes an acute infection with symptoms that fade within months, and hepatitis B, which commonly becomes chronic in children and in up to 10% of adults. HCV remained undetected for far longer because it replicates slowly and causes symptoms similar to other diseases. It was only when researchers at the National Institutes of Health (NIH) in Bethesda, Maryland, began to tease apart the causes of liver disease in the 1970s that they discovered that another infectious agent was involved.

HCV is transmitted through the blood, mainly via transfusions, shared needles and reused medical supplies. Sexual and mother-to-child transmission is much less likely than for HIV. In developed nations, most new infections occur in injection-drug users. In poorer countries, there are more reuses of medical supplies and the French government estimates that it screens the populace intensively for HCV, and the French government estimates that it

Pawlotsky and others note that there has been progress towards preventing HCV infection. This success has come in part because the rise in HCV infections coincided with that of HIV, and the HIV-related public-health campaign targeted practices (such as sharing needles) that also contributed to HCV transmission. Combined with introducing thorough screening of blood donations, health officials in the United States were able to lower the infection rate from as high institution listed, as several hundred thousand per year to about 20,000 per year now. Still, “20,000 a year is not a small number,” says Brian Edlin, an epidemiologist and infectious diseases specialist at the State University of New York Downstate College of Medicine in Brooklyn, New York. “It’s still a fire that’s spreading — not as quickly as in the past, but it’s spreading.”

According to Ward, HCV infections are on the rise in older teenagers and young adults. Of those already infected, the groups most at risk of becoming symptomatic in the United States are veterans, who have an infection rate at least three times that of the general population, and the resources to screen for HCV.

“One is a very low level of awareness of the severity of the problem — clinician knowledge of HCV seems to be inadequate no matter what country you’re in.”

Even when a country is acutely aware of its HCV problem, the best available options are barely adequate to the task. In France, where politicians were found guilty of distributing HIV-contaminated blood in the mid-1980s, officials are now trying to prevent a repeat with HCV. French public-health workers have been screening the populace intensively for HCV. It’s still a fire that’s spreading — not as quickly as in the past, but it’s spreading.”

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THE SPREAD OF HCV

The hepatitis C virus reaches across the globe with highest prevalence in north Africa and south Asia. A major challenge is tailoring treatments and vaccines to the various viral genotypes which affect treatment response.

PREVALENCE OF HEPATITIS C VIRUS INFECTION

- < 1.0%
- 1.0–1.9%
- 2.0–2.9%
- > 2.9%
- No data

HCV GENOTYPE DISTRIBUTION BY CONTINENT

- Egypt has the highest prevalence of hepatitis C with more than 14% of people infected.
- India’s hepatitis C epidemic is relatively mild thanks to a historically underdeveloped healthcare system.

Baby boomers (those born between 1946 and 1964). In fact, baby boomers, who make up about 30% of the US population, account for two-thirds of the people in the United States with HCV.

The potential healthcare burden these numbers represent is alarming. Over the past five years, the number of veterans with HCV who have liver cancer has tripled. Some Veterans Affairs hospitals now report more cases of liver cancer than colon cancer, says Janet Durfee, who directs nationwide public-health programmes for the Department of Veterans Affairs. By contrast, in the general population, colon cancer is about four times more prevalent.

HOPE FOR NEW DRUGS

Much about HCV remains to be fully understood. It remains a mystery, for instance, why some people infected with HCV never develop symptoms. About 15–20% of those infected with HCV can clear the virus without pharmaceutical help, and among teenagers and young adults, the proportion can climb as high as 50% (ref. 5). Of those who can’t fend off the virus on their own, most remain stable for decades, without any major symptoms. In the 10–15% of people who have symptoms, however, the virus causes cirrhosis: the liver becomes fibrotic and scarred, resulting in jaundice and a swollen abdomen, as well as a dangerous build-up of toxins in the blood and other serious complications. In some patients with cirrhosis, the disease advances slowly, but one in four — 2–4% of all HCV cases — develops liver cancer or liver failure.

“Getting away from interferon is everybody’s goal,” says Alan Perelson, a mathematical and theoretical biologist who specializes in HCV at Los Alamos National Laboratory in New Mexico. “It comes with side effects, cost,
inconvenience, injections, and the fact that not everybody responds to it.”

Changes are afoot. Two new antivirals are speeding their way to market. Boceprevir, made by drug giant Merck, headquartered in Whitehouse Station, New Jersey, and telaprevir, made by Vertex Pharmaceuticals, based in Cambridge, Massachusetts, are both inhibitors of an important viral protein, the NS3/4A protease. The drugs are designed specifically to attack HCV genotype 1, which is the most prevalent genotype, accounting for about 60% of global infections, and the least responsive to current treatment. They will supplement, but not replace, the standard interferon plus ribavirin therapy. Thus, they won’t eliminate the cocktail’s difficult side effects and may introduce new ones. The good news is that in phase III trials, each drug, in combination with the standard treatment, increased the cure rate of people with HCV genotype 1 from under half to 70%, while cutting treatment time in half for some.

“Just one new antiviral added to the standard of care will make a huge difference,” says Charles Rice, executive and scientific director of the Center for the Study of Hepatitis C in New York. “But the game’s not over. We’d really like to eliminate the current standard of care and replace it with something that works better and has fewer side effects.” There are several promising therapies at various points in the pharmaceutical pipeline (see ‘New drugs hit the target’, page S5). But there is a built-in delay in development: every new drug must be tested against the current, year-long, treatment regimen.

And drug developers are facing an elusive foe. The virus replicates so rapidly and is so error-prone when it does, that many genetic variations — including those that confer drug resistance — exist inside someone before he or she is diagnosed. The best strategy is therefore to throw multiple drugs at the virus at once, enough such that the pathogen would be unable to mutate to resist them all. Statisticians calculate such a feat would take two or three antivirals, all of which must target different components of the virus (a strategy similar to the drug cocktails used to fight HIV). The number of drugs needed “will depend on how hard it is for the virus to generate the number of mutations required to gain resistance,” Perelson says.

Further complicating the problem, because the risk factors for infection with HCV and HIV are similar, many people who are HIV-infected are also infected with HCV (up to 30% in the United States). For reasons that are not yet understood, this co-infected group has a lower cure rate and suffers from more side effects. Moreover, many of the antiretroviral drugs used against HIV can build up in the liver, poisoning the organ that the HCV drugs are working to save. And the new protease-inhibitor drugs have not yet been vetted in more than a few dozen co-infected patients. “The amount of information we have on those who are dually infected is abysmal,” says Thomas. “We’re going to have these treatments available this year and not have any idea on how to use them in combination with antiretrovirals.”

Most researchers and public health experts concur that, in addition to better treatments, the ultimate solution is a hepatitis C vaccine. “Otherwise, we’ll have infection from other parts of the world where therapies are not available,” Pawlotsky says. But vaccine development is challenging, and the virus has kept researchers guessing for decades already (see ‘A moving target’, page S16).

### OUT OF HIV’S SHADOW

When discussing HCV, comparisons with HIV are nearly unavoidable — both appeared on the communicable disease radar around the same time and both have similar modes of transmission. But the HCV problem cannot be solved by repurposing the agents developed to fight HIV, given the marked differences in the biology of these viruses. “Their differences are greater than their similarities,” says Miriam Alter, an epidemiologist at the University of Texas Medical Branch in Galveston. She notes that HCV has been endemic to human populations for centuries, and it is biologically much different from HIV.

The differences also stretch beyond biology and into public-health initiatives. The discovery of HIV led to a huge amount of funding for antiviral research and development around the world. “With hepatitis C,” says Thomas, “we haven’t even had widespread adoption of treatment here in the US.”

Even diagnosis of HCV infection (see ‘A testing journey’, page S20) has lagged far behind HIV. The CDC estimates that about 80% of HIV-infected people in the United States know they have the disease, but the figure for HCV awareness is about 30%. And worldwide, that number shrinks to an abysmal 5%. “We’re looking at an epidemic that is five times the size of the HIV epidemic, that spreads more quickly, that is treatable and ultimately curable. And yet, as a nation, we’ve got our heads in the sand,” says Edlin.

At the same time, it’s hard to deny that the field has made great strides in a short time. As Rice says: “In 1975, there was this agent causing all this disease, and nobody knew what it was. And here we are today and we can effectively treat a majority of people who are infected.” The research is headed in the right direction — but disease awareness still lags far behind. It will take a concerted effort and a huge national and international collaboration among public-health officials, doctors and governments to stop the raging epidemic before it burns through the limited resources of healthcare systems around the world.

Lauren Gravitz is a writer in Los Angeles, California.

4. Department of Veterans Affairs, Veterans Health Administration, Office of Public Health and Environmental Hazards and Public Health Strategic Health Care Group State of Care for Veterans with Chronic Hepatitis C (Department of Veterans Affairs, 2010).
New drugs hit the target

With two recently approved drugs and dozens more in the pipeline, hepatitis C treatment will improve over the next decade.

BY JANA SCHLÜTTER

When Charles Gore talks about some of his colleagues, there is more than a hint of urgency in his voice. Although he cleared his hepatitis C virus (HCV) infection after receiving the standard treatment, two of his staff at the World Hepatitis Alliance, an advocacy organization, recently had liver transplants. “And they are lucky,” says Gore, who is president of the alliance. “This treatment does not help about 50% of the patients who are infected with the most common form of the virus. So their liver becomes worse, and many of them cannot get a transplant. They are facing death.”

Around the globe, patients who have not been cured by the current treatment, a combination of interferon-α and ribavirin, are waiting for new drugs. So far, their doctors have had nothing to offer them but another 48-week-round of the same drug combination, which had its last upgrade in 2001 when researchers attached a molecule called polyethylene glycol to interferon-α. This ‘ pegylation’ allows interferon-α to stay in the body much longer, reducing the frequency of injections from three per week to one. But the side effects are just as harsh, including flu-like symptoms, anaemia and depression. And although the patient being treated may be too weak to work or enjoy family life, the virus often manages to survive and prosper under these conditions. At most, 20% of patients are cured by this second course of treatment. Still, there was no alternative.

This situation is about to change. Two powerful weapons against chronic HCV infection have been licensed: the protease inhibitors telaprevir, from Vertex Pharmaceuticals, based in Cambridge, Massachusetts, and boceprevir, from drug company Merck, headquartered in Whitehouse Station, New Jersey. When either drug is added to the current therapy, the cure rate increases for patients who have so far been spared the daunting year-long treatment: that is, ‘treatment-naïve’ patients. The drugs also offer hope to those increasingly desperate patients who have not been helped by the standard treatment: instead of around a 20% chance of a cure, these ‘treatment-experienced’ patients now have a 30–90% chance. “We are approaching a new era of management of this disease,” says Mark Thursz, a hepatologist at Imperial College London and current secretary-general of the European Association for the Study of the Liver (EASL).

The drug manufacturers have tailored these protease inhibitors to HCV genotype 1, one of at least six forms of HCV. Genotype 1 is particularly widespread in the United States and Europe and is one of the least responsive to the standard treatment. The clinical studies coming out now, Thursz says, “show that the new drugs can tame the pit bull terriers of the hepatitis C world: the genotype 1 viruses.”

In addition to telaprevir and boceprevir, there are dozens of compounds in the pipeline, and that’s only counting the ones that drug manufacturers are willing to disclose. These drugs target many aspects of the virus’s life cycle — the stages it goes through in the liver cell to reproduce itself. Used in combination, the new agents might be able to target all HCV genotypes at once, while improving the cure rate and preventing drug resistance from emerging. Although most of these drug candidates are being added to the current treatment, an interferon-free regimen has recently shown promise — a possibility that could substantially reduce treatment side effects and increase adherence.

DIRECT HITS

In the current regimen, interferon-α boosts the patient’s immune system, and ribavirin is a general inhibitor of virus replication. By contrast, the new drugs target HCV directly. Telaprevir and boceprevir block HCV’s NS3/4A protease. After an HCV particle attaches to and enters a liver cell, it releases its RNA, which is subsequently translated into a single polyprotein (see ‘The life of HCV’). This long chain is cleaved into functional proteins by NS3/4A, which acts like a pair of molecular scissors. Without the protease, functional viral enzymes and structural proteins are not generated, so HCV cannot complete its life cycle.

This March, the drug companies reported results of phase III clinical trials of telaprevir and boceprevir, each coupled with the current therapy, at EASL’s International Liver Congress in Berlin. Two-thirds to three-quarters of treatment-naïve patients with HCV genotype 1 are likely to clear the virus permanently. And treatment time is expected to be halved for patients in this group who have undetectable levels of virus after four weeks of treatment.

More hotly anticipated were the data for the treatment-experienced patients, including relapers, whose virus had become undetectable but rebounded after their previous treatment ended; partial responders, whose
viral load decreased by at least 99% but never became undetectable; and null responders, who previously had little success in fighting the virus. Telaprevir was tested in the Realize trial, which involved 662 patients from Europe and the United States. Adding telaprevir for 12 weeks to a 48-week-treatment course increased the cure rates from 24% to as high as 88% in relapers, from 15% to 59% in partial responders, and from 5% to 33% in null responders. Boceprevir was tested in 403 patients in centres across the United States and Europe in the Respond-2 trial. Adding boceprevir for 32–44 weeks caused the cure rate to climb from 29% to 69–75% in relapers and from 7% to 40–52% in partial responders. (Null-responders did not participate in this trial.)

“To have direct-acting antivirals against hepatitis C and to see such increases in cure rates is a huge step forward,” says Stefan Zeuzem, a hepatologist at the Goethe University Medical Center in Frankfurt, Germany, who was involved in both the Realize and Respond-2 trials. But these drugs are not cheap. “Cost will be a major issue,” he says. “However, we are preventing liver cancer and other end-stage liver diseases, which makes it worthwhile. We are aiming for a cure, not just a few more weeks to live.”

Both of these drugs also have side effects. More than half of the patients treated with telaprevir developed a rash, with 3–6% having a rash severe enough to halt treatment. Boceprevir is associated with anaemia (similarly to telaprevir) and can cause a metallic taste in the mouth, both of which affect nearly half of all patients. These problems are in addition to those caused by interferon-α and ribavirin, meaning that nearly every patient in the clinical trials suffered from at least one side effect. “It’s still a tough treatment,” says Gore. “For patients, it’s very important that clinicians manage these side effects well.”

If side effects cause patients to abandon treatment on the new regimen, this could lead to HCV developing resistance to the new drugs. The new protease inhibitors cannot be given alone and must be given with interferon-α and ribavirin to prevent protease-inhibitor resistance emerging. Thursz adds that as boceprevir and telaprevir are similar compounds, resistance to one will probably translate into resistance to the other (so-called cross-resistance), restricting future treatment options.

HCV is a highly mutation-prone virus, with many genetic variants present in any one host. Before treatment starts, variants that are resistant to a particular drug make up a minority of the viral population. Under selective pressure of the antivirals, however, these variants could become the dominant strains. “We understand resistance and have to manage it,” says Jean-Michel Pawlotsky, a hepatitis specialist at the University of East Paris in Créteil, France, and director of the French National Reference Center for Viral Hepatitis B, C and delta. He recommends that these new drugs should be administered at expert centres that can monitor resistance issues. “It is better to be well-treated than just treated,” he says.

Despite the high cure rates, not every HCV-infected patient will benefit from the new drugs. Possible drug–drug interactions are not yet fully understood. And there are no data for the many patients who are co-infected with HIV or for patients with end-stage renal disease, decompensated (or extremely advanced) liver cirrhosis or a recent liver transplant. Furthermore, telaprevir and boceprevir have been licensed by the US Food and Drug Administration only for treating HCV genotype 1 infection. As Pawlotsky says, “What we are seeing now is just the first step into the era of direct-acting antivirals. It will cause a real shift, but it’s not a full revolution.”

**COVERING EVERY ANGLE**

More than 50 other drugs are, however, in the research and development pipeline (see ‘Drug candidates for treating HCV infection 2011’). Many of these are in new classes — that is, they target different mechanisms — and can be combined to create antiviral cocktails, limiting the emergence of drug resistance. With so many new agents snapping at their heels, boceprevir and telaprevir might have a very limited time as the dominant new drugs, says Zeuzem.

Two other first-generation protease inhibitors are in phase III trials: TMC435, from Tibotec Pharmaceuticals, in Beerse, Belgium, and pharmaceutical company Medivir in Huddinge, Sweden; and BI201335, from pharmaceutical company Boehringer Ingelheim, headquartered in Ingelheim am Rhein, Germany. Both are taken once daily instead of three times, seem to cause fewer side effects and might even be more potent than boceprevir and telaprevir.

The second generation of protease inhibitors is expected to be led by Merck’s MK-5172, a compound that does not seem to have cross-resistance issues with other drugs of this class and might be effective across multiple genotypes. “We want to see if the resistance profile is robust enough that we can treat people who are failures from earlier generations of protease inhibitors,” says Keith Gottesdiener, vice president for hepatitis C clinical development at Merck. “That would be exciting if it was proven in the clinic.”

The pharmaceutical company F. Hoffmann-La Roche, headquartered in Basel, is about to start phase III trials of meritabine, which blocks the activity of HCV’s polymerase enzyme, NS5B. By mimicking the building blocks of RNA, meritabine is incorporated into newly formed viral RNA but prematurely terminates it, halting the life cycle.

Another protein generating immense interest as a drug target is NS5A. Its precise function is mysterious, but it seems to be involved in the replication, assembly and release of HCV.
A sample of some of the novel agents in development to target HCV

<table>
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<tr>
<th>Mechanism</th>
<th>Direct-acting antiviral agents</th>
<th>Host-targeting agents</th>
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<tr>
<td>Target</td>
<td>Inhibitor of polyprotein processing</td>
<td>Inhibitor of HCV replication</td>
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<td>NS3 or NS3/NS4A protease</td>
<td>NS5A</td>
<td>NS5B polymerase</td>
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<tr>
<td>Recently approved</td>
<td>Telaprevir (Vertex)</td>
<td>Bocceprevir (Merck)</td>
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<td>Phase III</td>
<td>TMC435 (Tibotec and Merck)</td>
<td>BI201335 (Boehringer Ingelheim)</td>
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<td>Phase II</td>
<td>ACH-1625 (Achillion)</td>
<td>BMS-790052 (Bristol-Myers Squibb)</td>
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<td>Phase I</td>
<td>GSXK336805 (Gilead/Sanofi-ema)</td>
<td>IDX320 (dienzo)</td>
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<td>Preclinical</td>
<td>ACH-1095 (Achillion)</td>
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BMS-790052, from biopharmaceutical company Bristol-Myers Squibb, headquartered in New York, was the first inhibitor in this class and is now in phase II trials. The pipeline is rapidly filling with others.

Cyclophilin A inhibitors block a host protein that is essential for viral replication. Candidates include alisporivir (DEB025), from drug company Novartis, headquartered in Basel, Switzerland, which is in phase III trials. In theory, targeting a human protein that HCV needs will render the virus' genotype or mutation status irrelevant and make it much less likely that resistant strains of HCV will emerge.

**FREE FROM INTERFERON**

There is also hope for patients who are not responsive to — or cannot tolerate — the backbone of triple therapy: interferon. This April at the International Liver Congress, Anna Lok, a hepatologist at the University of Michigan in Ann Arbor, presented data from a small phase IIa study of an interferon-free regimen in null responders. The study comprised patients on double therapy consisting of two classes of direct-acting antiviral: Bristol-Myers Squibb’s BMS-650032 (a protease inhibitor) and BMS-790052 (an NS5A inhibitor). These patients were compared with a cohort taking quadruple therapy, consisting of these two antivirals plus interferon-α and ribavirin. The quadruple therapy suppressed HCV in 10 out of 10 patients for at least 12 weeks after treatment, whereas the interferon-free double therapy suppressed HCV in 4 out of 11 patients, with 6 being null or partial responders.

The numbers might not seem great, but they are a start. “The potential for an interferon-free regimen is some of the most exciting news this year,” says Thursz. Without interferon-α and ribavirin, the virus was expected to rebound after treatment, but this occurred in only one case. “There is still a lot of work to be done. But this was a group of very difficult-to-treat patients with excellent outcomes. Although the numbers are small, I think this is the direction we can expect to go in the future.”

Indeed, this possibility has energized hepatitis C researchers. “People would have laughed at you if you suggested something like this five years ago,” says Zeuzem. “Now, we know that such a therapy might be available in another five to ten years.”

Many of the other drugs in the pipeline, such as the NS5B inhibitors, could also be candidates for an interferon-free regimen, says Paul Pockros, co-director of clinical research at the Scripps Translational Science Institute in La Jolla, California, who is involved in phase II studies of mercicitabine. Although mercicitabine is slightly less effective than the protease inhibitors, it seems to be a safe drug with a high barrier to resistance. “This one would be a good partner for a protease inhibitor,” says Pockros.

With all the excitement about new drugs, one would be forgiven for thinking that interferon has had its day. But there is also development on this front. Bristol-Myers Squibb has developed a variant called pegylated interferon-λ, which is designed to be more potent and safer than interferon-α. Interferon-λ docks with different receptors that are less common than the receptors for interferon-α. This interferon circumvents the bone marrow and therefore avoids anaemia and flu-like symptoms, so it might be a good partner for direct-acting antivirals.

With interferon-free regimens on the horizon, the question is whether a new interferon will be needed. But there are many potential pitfalls on the way to the clinic, and HCV is a very difficult virus to target. Researchers need as many options at their disposal as possible, says Zeuzem, “just in case.”

Jana Schlüter is a freelance journalist based in Berlin.
New drugs are generating much excitement, but a cure for all will take generations of therapies, argues Charles Rice.

The blood-borne hepatitis C virus (HCV) infects at least 130 million people worldwide. Over decades of chronic infection, patients are at risk of fibrosis, cirrhosis and liver cancer. Currently, HCV infection is treated with a weekly injection of pegylated interferon-α and a twice-daily weight-based dose of ribavirin. This standard of care, which has not changed for almost a decade, is considered suboptimal because of its long duration, side effects and inability to cure about half of all patients. In May this year, boceprevir, a first generation direct-acting HCV inhibitor, was approved for use by the Food and Drug Association. Patients and doctors have been waiting more than twenty years for this breakthrough, but the celebration should be tempered. Achieving a universal cure for HCV will require much more work.

The new drugs generating all the buzz are the inhibitors of the viral NS3/4A protease. Telaprevir (Vertex Pharmaceuticals, based in Cambridge, Massachusetts) and boceprevir (Merck, headquartered in Whitehouse Station, New Jersey) have improved the cure rates for both treatment-naïve patients and those who had failed standard therapy. A major caveat of the protease inhibitors, however, is that they must be used in combination with the existing standard of care. This is because the virus can easily overcome a single direct-acting antiviral. HCV replicates in a prolific and highly error-prone manner, leading to the rapid emergence of point mutations that confer drug resistance. The continued need for interferon-α and ribavirin is disappointing because the new agents worsen the problematic side effects of standard therapy, especially rashes for telaprevir and anaemia for both telaprevir and boceprevir. Furthermore, host factors that affect the outcome of interferon-α plus ribavirin treatment continue to be reflected in protease-inhibitor clinical trials, for example African-American ethnicity, advanced liver fibrosis and single nucleotide polymorphisms in the region of the IL28B gene — although, to be sure, their adverse impact is reduced.

It is imperative that the HCV drug pipeline be kept flowing. The goal, an interferon-α and ribavirin-free regimen, will require multiple drugs with diverse modes of action. Cocktails of targeted antivirals will make it more difficult for the virus to become resistant — a strategy analogous to highly active antiretroviral therapy against HIV. Early combination trials are under way and showing promise, but it will probably be two to three years before two direct-acting antivirals are approved in combination with the standard of care, and perhaps five years before the first interferon-α and ribavirin-free drug cocktails reach the clinic.

As second- and third-generation combination regimens for HCV are unveiled, it is important to consider all those who need them. First, the new drugs will have to be tested in diverse patient groups. With at least six genotypes and dozens of subtypes, HCV is one of the most variable viruses known. Most clinical trials have been conducted in the context of genotype 1 — the most common type in Europe and North America. Each drug regimen will need to be tested at several geographical sites to encompass the most prevalent local genotypes. Patient factors must also be considered when evaluating treatment efficacy. Patients with cirrhosis, those receiving liver transplants and groups who are co-infected with HIV or hepatitis B virus are among those with the most critical needs and have traditionally been the hardest to treat. How these patients respond to next-generation drugs has not yet been properly evaluated.

People at the highest risk of the HCV are among the most marginalized groups in society, such as injection drug users, prisoners and those living in endemic regions of the developing world. In parts of Asia and Africa, up to 10% of the population is infected with HCV; in Egypt, the prevalence of anti-HCV antibodies is as high as 15%. As newer, more expensive, treatment options become available, the gap between those who can afford treatment and those who cannot will widen. Advocates for HIV/AIDS care made strides in promoting surveillance, increasing education, reducing stigma, strengthening health infrastructure and implementing harm reduction programmes. Importantly, tiered pricing models for antiretroviral drugs were negotiated, which ensure lower prices in poor countries and help promote universal coverage. The HCV community can learn from the HIV experience, including the need for combination therapy and the importance of integrating education and prevention when deploying new therapies.

A cure is possible — a statement that can’t be made about many other chronic diseases. Direct-acting antivirals mark an important first step, but this is no time to lose momentum. Researchers in academia and industry need to keep working on the pipeline to ensure that all those infected with HCV can receive proper treatment, allowing this disease to fade into medical history.

Charles Rice is head of the Laboratory of Virology and Infectious Disease at The Rockefeller University in New York. 
email: ricec@mail.rockefeller.edu
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“Girl, you’ve won the lottery,” said Deborah Teeters’ doctor, when the results of her genetic test came back revealing two Cs at a spot among the 3 billion base pairs of her genome. Teeters, a retired child-welfare reform worker in North Carolina, had avoided treatment for hepatitis C for more than a decade because of its ugly side effects, including anaemia, fevers and severe depression. She also knew that for roughly half of all patients the 48-week regimen doesn’t work. But two Cs means the odds are in her favour. She is ready to give it a shot.

Hidden within the scratch card of our genomes lie clues to how each individual uniquely responds to stress, disease and medication. If single ‘letter’ variations, called single nucleotide polymorphisms (SNPs), with high impact can be found, then doctors might be able to use this information to personalize patient care, and researchers could delve into the function of the affected genes to better understand disease and improve therapies.

Hepatitis C now leads the movement to combine genomics and medicine, following the discovery of a SNP near the gene IL28B. In this location, each person has either a cytidine (C) or a thymidine (T) nucleotide. And, as everyone inherits one IL28B gene from each parent, there are three possible combinations: CC, CT and TT. Patients with two Cs tend to clear the hepatitis C virus (HCV) when treated, whereas a CT or a TT genotype correlates with a poorer response (see ‘Lucky Cs’).

A test for this SNP now helps patients decide whether to undergo treatment — which currently consists of a year-long course of interferon-α injections plus multiple daily oral doses of ribavirin — or to wait until improved drugs hit the market. And pharmaceutical companies are interested in using the test to tailor their new drugs to specific populations.

In this way, hepatitis C is a success story among those who use genome-wide association studies (GWAS) to search the genome for SNPs that are clinically relevant.

“IL28B was a fantastic hit because nothing had ever proved as useful in GWAS before,” says Ellie Barnes, a clinician scientist at the University of Oxford’s Nuffield Department of Clinical Medicine, in the United Kingdom. “There have been lots of genes associated with diseases, but nothing else I know of has been put to use in the clinic and in clinical trials.”

It’s been a whirlwind journey. IL28B SNPs were first linked to treatment response in late 2009 (refs 1–3) — less than a year later, doctors and pharmaceutical companies were ordering IL28B SNP tests. Based on the C/T SNP1, the first test was offered for about US$150 in July 2010, by LabCorp, a diagnostics company based in Burlington, North Carolina. Since then, “the test has been going gangbusters,” says John McHutchison, a co-author of one of the IL28B papers’ who is now at biopharmaceutical company Gilead Sciences (Foster City, California). Indeed, in April 2011, another company, Quest Diagnostics (Madison, New Jersey), launched its own version of the test.

For the majority of HCV infections in the West, the IL28B SNP is a more accurate predictor, or biomarker, of an individual’s response to current drugs than existing markers such as viral load, ethnicity or body mass. Doctors may advise TT genotype patients to wait for better drugs as long as their liver looks healthy, McHutchison says. Or, if the side effects begin to distress a CC patient undergoing therapy, a doctor might encourage them to persist because the chance of success is high.

As more genetic factors are uncovered, not only will doctors be better placed to...
recommend treatment but also researchers will learn how our immune system interacts with HCV.

STACKING THE DECK

Even before uncovering the significance of IL28B, there were hints that response to HCV treatment had a genetic component. Response varies predictably with a patient's ethnic group: after treatment, only 20% of African Americans successfully cleared the virus compared with 50% of people of European descent and 75% of individuals of Asian descent, explains David Goldstein, director of the Center for Human Genome Variation at Duke University Medical Center, in Durham, North Carolina, and co-author of one of the IL28B papers1. “Some people thought these variations were due to differences in behaviour, lifestyle, health care or diet, but I always suspected genes were behind it,” says Goldstein. “When there’s a difference this big between individuals from separate ancestries, to me the simplest explanation is a difference in genetic frequencies.”

Indeed, Goldstein says, the C/T variant near IL28B accounts for at least half of the discrepancy between the response of African Americans and other HCV-infected patients. Whereas only about 13% of African Americans carry the lucky CC combination, about 51% of European-Americans and more than 90% of East Asians do. But other factors are clearly in play.

Two recent additions to the HCV biomarker tool kit are ITPA and IP-10. A GWAS at Duke found an association between anaemia in response to ribavirin treatment and two variants in ITPA2. The ‘protective’ ITPA variants reduce the activity of the enzyme inosine triphosphatase (ITPA). In the presence of ribavirin, ITPA indirectly contributes to red blood cell instability, so its disruption can protect against anaemia2. Predicting this outcome might be beneficial because anaemia causes up to 15% of patients to cease or reduce their treatment.

IP-10 (also called CXCL10) is a cytokine that attracts immune cells, and its levels naturally vary among individuals. Patients with high levels of IP-10 in their blood are less able to clear HCV when treated than patients with low levels. One explanation for this paradox is that some of the abundant IP-10 is in a form that blocks the signals directing other immune cells to the site3.

Then there are other clinical clues, such as the patient’s age and whether the patient has been treated before. Together, these markers help predict the likelihood that an HCV-infected patient will comply with treatment and be cured with the existing regimen.

But the ground is about to shift, with the arrival of two medications: boceprevir, from the drug giant Merck (Whitehouse Station, New Jersey), and telaprevir, from Vertex Pharmaceuticals (Cambridge, Massachusetts). Trials of these drugs were in progress when the IL28B reports were published. Leaders at both companies say they immediately recognized the reports’ significance, but it was too late to divide trial subjects by IL28B status. So the companies tested willing participants after the trials had begun and retrospectively analysed the data.

SHAKING THE STATS

In late March 2011, Vertex and Merck presented results of their late-stage clinical trials, including data on IL28B status, at the International Liver Congress in Berlin. For all IL28B genotypes (CC, CT, TT), more patients were cured with the standard combination of interferon-α and ribavirin plus either boceprevir or telaprevir than with the standard treatment alone. In particular, TT individuals receiving treatment for the first time had much better response rates — 73% were cured by the telaprevir-containing regimen compared to about 23% with the standard regimen. But these results should be considered with caution, as the patients who agreed to be genotyped could represent a biased population.

With each drug entering clinical trials, the ground is one example of how genome-wide association studies have catalysed a great deal of work on how the body fights infections. The C/T variant near IL28B doesn’t seem to alter the amount of protein produced. Instead, it must change the protein’s interaction with molecules in the interferon-α pathway, the virus, immune cells or other immune-related genes. Observing immune responses and viral loads in people with different IL28B genotypes provides some clues. At the International Liver Congress, Zobair Younossi, hepatologist and vice president for research at Inova Health System, a large healthcare provider based in Falls Church, Virginia, reported that, before treatment, patients with the unfavourable CT and TT genotypes express more genes involved in immunity than CC patients. He speculates that this strong pre-treatment activation undermines the body’s response to the drugs, which would explain why these patients are less able than CC patients to clear the virus. If he’s right, temporarily suppressing specific immune responses before treatment could help those with a CT or TT genotype.

With IL28B, scientists have made good on a decade-old promise that genomic research will improve clinical care. Less than a year has passed since the IL28B test hit the market, and the biomarker is already affecting patients’ lives. “I’ve been terrified of this treatment for ten-plus years,” Deborah Teeters says, “and now I’m not as afraid, knowing I’m CC.”

To researchers, it’s a symbolic victory. “This is one example of how genome-wide association studies have the power to uncover genetic markers for disease propensity and treatment response,” says McHutchison. “There needs to be a groundswell of activity to make people understand the potential of genomics in medicine.”

Hepatitis C will be at the front of the wave.

Amy Maxmen is a freelance writer based in New York City.

Recognizing resistance

The hepatitis C virus is endemic among injection drug users, who could harbour treatment-resistant viruses. We need to adapt to this reality, says Diana Sylvestre.

The first antiviral agents that act directly on the hepatitis C virus (HCV) are about to hit the market. Healthcare workers have been awaiting the release of these new medications for some time, in the hope that treatment response rates would improve, even in populations of patients who are challenging to treat. But underneath the glow of anticipation lies a concern about poorly characterized risks, including the emergence of drug-resistant viral strains. The real-world impact of this risk is unclear as most of those who contract the virus do so through injection drug use and are disregarded from clinical trials.

The new protease inhibitors can elicit resistance even in patients who follow dosing regimens. But when corners are cut, risk rises. Shortening treatment, as new regimens promise to do, might reduce the burden of side effects. But the day-to-day misery will be worse with triple regimens than with the standard dual treatment, and it is important to appreciate the human tendency to reduce or skip doses of medications that make us feel ill.

Injection drug users are more complex patients: many have an unstable housing situation, unreliable transport or subject to prescription refill delays owing to insurance company bungling, which they are poorly equipped to deal with. They might be arrested and jailed during treatment. So, even though studies have shown that injection drug users have similar medication compliance rates to non-drug users, external circumstances may prevent the medication fidelity that is expected and needed.

So far, modestly reduced adherence to the interferon-α and ribavirin therapy has not led to viral resistance. Taking only 80% of the prescribed interferon and ribavirin dosages for 80% of the projected duration of treatment is sufficient to achieve optimal response rates. This allows those who treat injection drug users (including me) enough latitude to be successful. We have been able to reduce the burden of HCV in those who are most at risk of transmitting it.

Unfortunately, there is no such information on new treatment regimens. It is unclear at what point reduced adherence may become a problem. The virus rapidly mutates, so the antiviral ‘pressure’ exerted by the medication needs to be maintained so mutant viruses are constantly destroyed. Such protease-inhibitor-resistant strains can persist for at least three years after the withdrawal of medication. And the conformational changes that underpin resistance to one protease inhibitor may also confer resistance to other inhibitors of that protease — a phenomenon called class resistance. And worse: if active injection drug users become reservoirs of protease inhibitor resistance, these viral strains could predominate, requiring the kind of therapeutic arms race that we see in other infections such as HIV and Staphylococcus aureus.

Regulators should require that clinical trials consider current or former injection drug users. This is not currently being done. The US Food and Drug Administration (FDA) Guidance for Industry document encourages trial sponsors to initiate trials early in drug development for “special populations” with unmet needs: transplant patients, people co-infected with HIV and HCV, and those with compensated, or severe, cirrhosis. The document fails to mention injection drug users. It is as though they don’t exist. If diabetics or out-of-care asthmatics were at risk, the approach would be different. Instead, the FDA has turned its back on the majority population with HCV and is approving new drugs despite having almost no understanding of their potential to cause long-term harm.

Because HCV affects those on the fringes of society, large-scale treatment studies have not been representative of the face of the disease. Their doctors are not invited to enroll them in trials. Therefore, little is known about which patients are good candidates for treatment, the importance of adherence to the treatment regimen and the outcomes in the real world — this ignorance leaves addicted HCV patients subject to the vagaries of a medical system that might not welcome them. This is unacceptable from both a humanist and a public-health standpoint.

It is time that regulators, pharmaceutical companies and healthcare workers come together to recognize the fact that many patients with HCV are injection drug users. These patients must be included in safety, tolerability and efficacy trials; regulatory studies should include clinics where HCV-infected drug users are seen. And study investigators should be more representative of the kinds of doctors that usually care for these patients.

The new therapies raise the possibility of eradicating hepatitis C. But that won’t happen unless the key parties in this medical drama develop a more realistic approach to understanding and treating this disease.

Diana Sylvestre is an assistant clinical professor of medicine at the University of California, San Francisco. e-mail: diana.sylvestre@ucsf.edu


Diana Sylvestre informs her patient that the hepatitis C virus has re-emerged six months after treatment.

PERSPECTIVE
Egypt is a hepatitis C anomaly. Globally, roughly 1 person in 50 is infected with the hepatitis C virus (HCV). In Egypt, a recent study found that about one person in seven of Egypt’s 83 million population tested positive for antibodies against HCV, indicating that these individuals have been infected with the virus at some point. However, nearly one person in ten carries its viral RNA and is therefore chronically infected. This represents a huge viral reservoir that is fuelling the spread of the disease among Egyptians, mainly through hospitals and clinics (medical and dental; private and public).

Firm data for the infection rate are hard to come by. A 2010 study estimated that more than half a million people are newly infected each year. However, the Egyptian Ministry of Health and Population (MOHP) puts the number at 100,000 per year. Both numbers should be much lower, says Laith Abu-Raddad, an epidemiologist at the Doha-based Weill Cornell Medical College in Qatar and co-author of the 2010 study. He questions why there are so many new cases of a preventable infection each year.

Not only is the Egyptian HCV problem one of size, but the genotype of the virus in circulation is one that is not commonly found in the rest of the world. There is no guarantee that it will be confined to Egypt. Cheaper travel and increased migration means that Egypt’s HCV problem is already starting to spread to Europe and the rest of the world.

**SUCCESS BREEDS FAILURE**

Egypt’s current problem with hepatitis C arose after an earlier — successful — health campaign against a different type of pathogen. Schistosomiasis is a disease caused by a parasitic worm that can burrow through skin and lurks in contaminated water. The worm then travels to the lungs and liver, where it matures and moves to other organs. During the early part of the twentieth century, schistosomiasis was highly prevalent in Egypt, especially in rural areas, and was a major cause of liver disease. From the 1950s to the early 1980s, the MOHP and the World Health Organization (WHO) led a large-scale campaign to control the disease. Millions of people were treated with intravenous injections of tartar emetic, before an oral drug replaced this standard of care across the country in the 1980s.

Although the campaign helped reduce the prevalence of schistosomiasis, this came at a price. At the time, little was known about hepatitis or about the causative viruses and their transmission. Reuse of glass syringes and lax sterilization practices caused widespread infection with HCV, which by the 1990s had replaced schistosomiasis as the primary cause of liver disease in Egypt.

The virus that was spread by this programme has a different genotype from HCV in most other countries. Egypt — and the Middle East more generally — is a stronghold for genotype 4. By contrast, about 75% of HCV infections in Europe and the United States are of genotype 1. Consequently, most research conducted in the West has gone into the control and treatment of that genotype; there have been comparatively few studies on how to improve the treatment of patients with genotype 4.

The dominance of genotype 4 in Egypt complicates the task of treating the disease. “There are no antiviral drugs being developed locally to combat genotype 4,” says Alaa Ismail, head of the liver research unit at Ain Shams University in Cairo. The treatments available to people with hepatitis C in Egypt are therefore imported from the West and have been extensively tested only on genotype 1. “All the drugs that we get from overseas must undergo clinical trials here again,” he says.

The best estimate for genotype 4 is that only 60% of those treated clear the virus completely. Although this is better than the cure rate for genotype 1 (at about 50%), it is still inadequate and new treatments are needed. But most Egyptians struggle to afford even the existing drugs.

**GLOBAL HEALTH**

Egypt has the highest prevalence of hepatitis C worldwide. And the epidemic will soon peak. Prevention demands political will, ample funding and a change in mindset.

**BY MOHAMMED YAHIA**

A uniquely Egyptian epidemic

A Zabbaleen boy, from a group traditionally employed to collect rubbish, is tested for hepatitis C in Cairo.
around US$3,500 — well above the Egyptian median income of US$2,070 per person each year.

**PREVENTION IS THE BEST CURE**

The MOHP has two programmes in place to tackle HCV infection — one targeted at treating chronic, symptomatic patients, and one aimed at prevention.

Through the treatment programme, the MOHP provides free or subsidized treatment for the millions of infected people who cannot afford the drugs. It is one of the largest burdens on the healthcare system in Egypt. Yet despite the large number of patients and the high cost of the treatment regimen, the MOHP argues that it is more cost effective than treating patients after they develop serious complications such as liver cirrhosis or liver cancer.

DeWolfe Miller, an epidemiologist at the University of Hawaii in Honolulu and one of the first to discover the Egyptian epidemic, in 1992(ref. 4), says: "There are national centres for HCV treatment, but there has been criticism regarding access and the quality of drugs used. I estimate that these programmes reach approximately 30% of the total number of Egyptians who are in need of treatment." Miller contends that diverting some of the MOHP’s resources from treatment to prevention would be a better use of funds. "What is frequently misunderstood is that treatment, however important that may be, does not reduce or prevent transmission," he says.

At the core of the MOHP’s prevention programme are public awareness campaigns, mainly run through television programmes and posters in hospitals, which have been in place for about ten years. According to Ismail, who was also director of the ministry responsible for the hepatitis C programmes — the National Hepatology and Tropical Medicine Institute (NHTMI) in Cairo — until 2006, the national centres for HCV have seen a decrease in the number of new infections over the past few years. This drop "can only be attributed to the awareness campaigns," Ismail says. "This is a socioeconomic disease, and while 60% of infections happen in hospitals and clinics, the rest are down to bad social practices, such as the sharing of razors at barber shops or the sharing of home diabetes testing equipment."

Miller, however, challenges the effectiveness of the prevention efforts. He points out that the virus continues to spread in Egypt. "It is the responsibility of all healthcare professionals to provide safe healthcare. Indeed, he says, health-care professionals could take a big step towards slowing the spread of HCV in Egypt by simply maintaining clean facilities. “The HCV is so fragile that it can be disinfected with soap and water.”

The MOHP is taking action on this front. In 2008, it began a new campaign, with two major elements. “The first is education, where we regularly teach hospital staff about infection control,” says Mohamed Ezz El-Arab, head of the tumour unit at NHTMI. “Second, every hospital now must have an infection control committee which has clear authority to monitor what is going on in the hospital.”

Furthermore, HCV and infection control is now an important course that is taught in all medical universities, unlike the brief mention it received a few decades ago. There are also meant to be regular inspections of public hospitals and clinics to ensure that they meet the infection control standards set by the WHO and that proper waste-disposal protocols are in place.

Critics like Miller say that actions speak louder than words. He remains unconvinced of the programme’s value or of its implementation. There have been recorded instances, he says, where public hospitals have dumped their waste “directly, without treatment, into the solid waste stream”, violating WHO specifications. “This is a scandal.”

Just last October, the Egyptian weekly magazine *Rose al-Yousef* reported that dialysis filters had been found in the non-medical waste disposal in front of a university hospital. Rubbish scavengers had been washing and reselling them for a fraction of their original price. In 2008, the Egyptian daily *Al-Masyr Al-Youm* reported that truckloads of medical waste, including blood bags, had been delivered to garbage collectors for reuse.

Disposing of medical waste in this way is highly unsafe and risks passing on the virus. Medical waste disposal is “better controlled in Cairo now,” says Ezz El-Arab. “But while we can follow-up on what is happening in Cairo, the problem is in rural areas further away where monitoring is hard.”

**THE REVOLUTION GOES VIRAL**

Measuring the success of these HCV programmes is hard because there are no objective data available. “Only those in the MOHP have any information on the status of this programme,” Miller says. Without good data, it is not possible to verify whether the rate of new HCV infection in Egypt is decreasing. And even if there has been a drop in the rate, the overall level of infection is still much higher than anywhere else in the world. It can take 20 to 30 years of HCV infection before people develop serious complications. So the worst effects of the epidemic will surface over the next few years.

There is a ray of hope. The MOHP is part of the government established by the former President Hosni Mubarak. Miller suggests that, after the popular revolution in early 2011 that toppled Mubarak, there may be an opportunity for implementing better prevention programmes as many of the ministries undergo changes. “Post revolution means that HCV prevention should and can be accomplished by non-governmental, non-profit organizations,” he says. “The MOHP has to come clean with its failure to prevent or reduce HCV transmission.” At the same time as creating a new government, perhaps the revolution will also offer a uniquely Egyptian solution to the HCV epidemic.

Mohammed Yahia is editor of *Nature Middle East*.

The murine candidate

Small animals that mimic human hepatitis C infection will help researchers pinpoint weakness in the viral life cycle.

BY ELIE DOLGIN

The hepatitis C virus (HCV) is hard to study. Most of what researchers know about how it multiplies comes from cell-culture systems. Such cellular set-ups have proven invaluable for developing new drugs, including protease inhibitors and polymerase inhibitors, which prevent the virus from replicating its components inside the cell. Yet these cell-based systems fail to capture other important parts of the viral life cycle, such as the step before replication, when the virus attaches to liver cells and gains entry. What’s more, cell-culture systems cannot reproduce the interaction between the immune system and the virus nor can they recapitulate entire organs so that liver pathology can be studied. For these reasons, researchers interested in how the virus causes disease have long sought a small-animal model.

Common laboratory animals, including rodents and most primates, are not susceptible hosts for HCV. Scientists have therefore had to settle for chimpanzees, which, like humans, are vulnerable to chronic HCV infections. However, “for ethical and economic reasons, the chimp is a terrible model,” says Matthew Evans, an HCV researcher at the Mount Sinai School of Medicine in New York. Research involving chimpanzees is banned in many parts of the world, including Europe. And in most places where experimentation with human primates is allowed, laws against euthanizing chimps require investigators to fund the animals’ long-term care — a prohibitively expensive commitment.

That’s where a colony of ordinary-looking black mice running around in cages on the fourth floor of the Rockefeller University Comparative Bioscience Center in New York comes in. These animals might not look special, but they have been engineered to express either a pair or a quartet of human genes and, as such, are the first small animals with fully functioning immune systems that are prone to HCV infection. Using these models, “you can actually now look at hepatitis C virus entry in vivo,” says Rockefeller immunologist Alexander Ploss, who developed the animals together with Charles Rice, executive and scientific director of the Center for the Study of Hepatitis C in New York.

These mice, and others like them, could provide a cheaper, more robust and less ethically fraught route to HCV drug and vaccine discovery.

THE HUMAN SIDE

Getting to this point has been a hard slog. In the years immediately after the virus was first described in 1989, many research teams developed transgenic mice carrying one or more genes encoding HCV proteins. Thus it was possible to study HCV-induced liver pathology without infecting mice with the virus. This approach still has some proponents. Last year, a team led by Matti Sällberg, a viral immunologist at the Karolinska Institute in Stockholm, used mice expressing the viral protease and showed that treatment with a drug targeting the cytokine tumour-necrosis factor-α led to improved liver function.

But the approach is highly artificial, leading to overexpression of the introduced viral genes and ignoring the rest of the viral life cycle. Over the past decade, most researchers have moved away from this set-up in favour of systems that involve infecting animals with the virus.

The first such model was reported ten years ago by a team led by transplant surgeon Norman Kneteman at the University of Alberta, in Edmonton, Canada. Kneteman’s group engineered mice to express a gene that kills off the animals’ own liver cells, which aren’t susceptible to HCV infection; in their place they transplanted human liver cells, which are. These mice with humanized livers could be infected with HCV. “This was the first [mouse] model that actually allowed HCV infection for prolonged periods of time by the normal route,” says Kneteman.

These animals have proven useful for testing many candidate drugs. For example, a Japanese team led by Hiroshima University’s Kazuaki Chayama treated Kneteman’s liver transplant mice with a combination of new drugs: the protease inhibitor telaprevir (from Vertex Pharmaceuticals, based in Cambridge, Massachusetts) and the experimental polymerase inhibitor MK-0608 (from drug giant Merck, headquartered in Whitehouse Station, New Jersey). Late last year, the team reported that this combination eliminated the virus from the animals after a month of therapy and prevented the emergence of drug resistance, which often arises in mice and humans treated with either drug alone.

But to facilitate the human tissue transplant, the mice must be engineered to lack components of their immune system. The animals are thereby rendered poor models for testing drugs that alter the immune system, known as immunotherapies. Generating these mice also presents special difficulties. For one,
researchers can’t breed chimaeric animals. And the mice are sickly because of the liver toxic gene.

Two recent transplant models of HCV infection provide improvements over Kneteman’s mice\(^6\). Both types of mouse are less frail because of technical workarounds that allow researchers to introduce the liver deficit later in life. The model developed by Lishan Su, an immunologist at the University of North Carolina at Chapel Hill, in collaboration with Ploss and Rice at Rockefeller, also involves transplanting human blood stem cells into the animals to reconstitute a human-like immune system\(^7\). Of all of the published reports, says Su, “this is the only one that has both the immune system and the human liver in a chimaeric animal”, creating a living platform for testing vaccines and immunotherapies in a human-like model.

Even though Su’s mice generate a human T-cell response against the virus when infected, they still lack a complete immune system. “What we need now is a mouse — an immunocompetent, normal, mouse — that can be infected by a hepatitis C virus capable of replicating, spreading and initiating an immune response,” says Frank Chisari, a virologist at The Scripps Research Institute in La Jolla, California. “We are light years away from that because that virus does not like to infect or replicate in mouse cells.” But scientists are getting closer.

**ENTRY LEVEL POSITION**

To gain entry into liver cells, HCV hijacks four proteins. Although mice naturally produce these proteins, the human versions of two of them are needed for viral entry\(^8\). The black rodents at Rockefeller are the first animals into which the required human entry factors have successfully been introduced. “This has a lot of applications,” says Ploss. “Right now, it’s useful to measure HCV entry and potential entry inhibitors.”

“This is a big advance,” says Michael Houghton, a virologist at the University of Alberta, who co-discovered HCV more than 20 years ago. “It’s been difficult to do vaccine research for hepatitis C because of the lack of an animal model other than the chimpanzee. Now we can start using different vaccine strategies in mice to see which are best at eliciting a protective response.”

Ploss’s mice are the first such animals with a fully intact immune system that are susceptible to the viral infection. But the infection stops after cell entry: the virus does not seem to replicate. “You can recapitulate HCV entry,” says Ploss, “but replication is still very inefficient and not detectable by conventional methods.” So the big challenge now remains identifying whether additional human factors are needed to achieve the next step of the HCV life cycle in mice.

After replication comes assembly, when the viral components are gathered into new infectious particles that will be released from the cell and invade other cells. Fortunately, this final stage in the viral life cycle seems to be possible in mouse cells without introducing any human proteins, according to research presented at this year’s International Liver Congress, in Berlin, by Ralf Bartenschlager, a molecular virologist at Heidelberg University in Germany. If the barriers to replication can be overcome, Bartenschlager says, it should be straightforward to get a full infection cycle going in a mouse. “We have the early steps; we have the late steps; the big black box now is the step in between.”

It took more than a decade for scientists to deduce the factors needed for HCV cell entry. But Thomas Baumert, a hepatologist and virologist at the University of Strasbourg in France, is confident that the community will solve the problem of replication much faster. “We have better model systems now, so I think we can advance more rapidly.” Within five years, he predicts, “it will be possible to produce transgenic mice for the entire viral life cycle.”

Rice is equally confident this approach will work — but he is hedging his bets. Even such a model would have its drawbacks, he says, because the more mouse-like the model, the further removed it is from the human system. That’s why even as his lab is aggressively pursuing a transgenic animal, he maintains active collaborations to develop other models, including new transplant chimaeric mice with humanized livers and immune systems. Other researchers are looking to animals that provide the natural susceptibility of primates without the ethical baggage (see ‘The turn of the shrew’). “All of these things should be pursued in parallel,” Rice says, “because we really don’t know which of these models is going to be the best for a given application.” And so Rice and others continue to try and build a better mouse to help the research community beat a path to new HCV treatments.

**THE TURN OF THE SHREW**

*Unusual model isn’t persuading researchers of its practicality*

Although most of the work developing small-animal models of hepatitis C virus (HCV) infection has focused on mice, some research teams have advanced an alternative model: the northern treeshrew (Tupaia belangeri). This squirrel-shaped animal shares a common ancestor with apes and is the only non-ape species known to be naturally susceptible to HCV. Last year, the first longitudinal analysis of HCV-infected tree shrews showed that, over the course of three years, the animals developed chronic hepatitis, fatty liver degeneration and liver cirrhosis\(^7\). “It’s very similar to HCV infection in human beings,” says study co-author Kyoko Tsukiyama-Kohara of Kumamoto University in Japan. But few research teams have managed to establish long-term infections in the animals. And given the limited track record of tree shrews in drug discovery, most scientists agree that more traditional lab animal models of infection, such as mice, are needed. “If you’re going to take a multimillion dollar drug and do your final trial before you go into humans, you need to have a reproducible model,” says Robert Lanford, who has studied HCV in chimps for more than 20 years at the Texas Biomedical Research Institute in San Antonio.

![The northern treeshrew, a natural host to hepatitis C virus, is proving an unpopular model of infection.](image)

Elie Dolgin is a news editor with Nature Medicine in New York.

A moving target

The hepatitis C virus has a set of cunning ways to evade immunity, but researchers are turning the immune system on it.

BY MICHAEL EISENSTEIN

The hepatitis C virus (HCV) dodges the immune system with devilish resourcefulness. Its vaunted genetic variability is an obvious advantage in escaping recognition by antibodies and T cells. But the virus also takes the fight directly to the host by actively suppressing the innate immune system, a key early mechanism in response to infection. In parallel, HCV uses diverse stratagems to mask its surface from antibodies that might neutralize infection. Recent evidence suggests that when all else fails, HCV hides — creeping directly from one liver cell to another, without exposing itself to the immune system. “It’s a wily operator and will not be easy to beat,” says Genevieve Inchauspé, a virologist at the University of Alberta in Edmonton, Canada, who co-discovered HCV in 1989.

Given these facts, one might expect HCV vaccine research to be an exercise in futility. But the minority of patients who banish the virus during acute infection offer hope that the immune system might be coaxed into rising to the challenge. “If somebody has recovered from a primary HCV infection, any subsequent infection is much milder, and they tend to clear the virus far more quickly,” says Marian Major, a virologist with the US Food and Drug Administration. “This protects the patient from chronic infection, which is the goal we need to meet for any HCV vaccine.”

Accordingly, the most aggressively pursued — and clinically advanced — research has focused on the development of therapeutic vaccines that can beef up an otherwise inadequate immune response and treat chronic disease. Prophylactic vaccines are also in development, but they face economic, ethical and social problems, on top of daunting scientific challenges. However, both approaches need to overcome a common problem: HCV is a wily operator and will not be easy to beat.

CALLING IN FOR BACKUP

Several companies are actively testing therapeutic vaccine candidates, most of which use a non-pathogenic viral vector that presents HCV proteins to the immune system. For example, French biopharmaceutical company Transgene, based in Illkirch Graffenstaden, is adapting the vaccinia virus, used in the smallpox vaccine, to provoke an immune response against a trio of HCV targets. In early clinical trials, Transgene’s TG4040 vaccine by itself achieved a modest reduction of viral load in chronically infected patients. Transgene recently started a phase II study to further assess TG4040’s efficacy in combination with the standard antiviral regimen of interferon-α plus ribavirin.

Instead of using a vector, the Swedish company ChronTech Pharma, based in Huddinge, Sweden, vaccinates patients with naked DNA molecules encoding HCV genes. DNA vaccines are considerably cheaper to manufacture than vector-based vaccines, although their track record is patchy. But, by using an electrical current to pulse DNA directly into muscle tissue, ChronTech has been able to markedly improve DNA uptake while eliciting a strong local immune response. “For patients who went through the vaccine trial and were then put onto standard care, their virus disappeared very rapidly, and they also had an unusually high cure rate,” says ChronTech co-founder Matti Sällberg, a viral immunologist at the Karolinska Institute in Stockholm. Indeed, five of six patients treated with ChronVac-C in conjunction with a standard drug regimen successfully eliminated HCV infection (relative to about half of all patients with existing drugs alone), and in March the company received approval for a phase II trial.

Both Transgene’s and ChronTech’s vaccines stimulate the cellular immune response — the first stage of the adaptive immune response, which kicks in after innate immunity (see ‘HCV versus the immune system’). In the cellular immune response, killer T cells destroy infected liver cells when they recognize surface features, known as epitopes, that indicate the presence of virus. Cellular immunity seems to be the front line in preventing progression of acute infection. “Spontaneous resolvers are those who elicit early and broad cellular immune responses against multiple epitopes,” says Houghton.

After the cellular immune response comes the humoral response, in which B cells secrete antibodies that can bind to and possibly neutralize HCV. The importance of humoral immunity in beating back acute HCV infection remains murky. “We need to learn a lot more about whether neutralizing antibodies are important,” says Genevieve Inchauspé, head of the Infectious Diseases Department at Transgene. Helper and killer T-cell-oriented therapies have shown some effectiveness in humans, and there is evidence that HCV might encounter problems in eluding T-cell recognition. Although the virus can acquire mutations that allow it to escape many immune-system traps, the mutations it requires to avoid T cells are detrimental and “actually reduce viral fitness,” says Sällberg.

Yet even the best therapeutic vaccine candidates induce reactions that fall far short of those of spontaneous resolvers. Most ongoing trials therefore add these experimental therapies to the current standard treatment, but the existing regimen is notable for its nasty side effects. “The ultimate goal would be to be able to replace interferon and ribavirin with a vaccine,” says Inchauspé, “or perhaps reduce the

VACCINES

The hepatitis C virus attacks liver cells, which can lead to cirrhosis and cancer.
PREPARED FOR THE WORST

As safer and more effective drugs approach the marketplace, thus covering the therapeutic front in the battle against HCV, many vaccine developers are trying to address the traditional objective of vaccines: preventing disease from taking hold in the first place.

While working at the biotechnology firm Chiron, later acquired by Swiss pharmaceutical firm Novartis, Houghton managed the team that developed the first preventive HCV vaccine candidate, based on an injection of purified recombinant viral envelope proteins. This Chiron/Novartis vaccine was designed to elicit the production of antibodies while stimulating helper T cells, which in turn stimulate killer T cells and thus promote cellular immunity. In preclinical studies, significantly fewer vaccinated animals exhibited chronic infection relative to unvaccinated controls after exposure to HCV\(^1\). In phase I trials, human volunteers responded to vaccination with a strong helper T-cell response while producing detectable levels of antibodies with the capacity to neutralize diverse viral subtypes\(^4\).

Although Novartis developed a plan for a phase II trial to assess the vaccine’s protective efficacy, work lost momentum after Houghton’s departure in 2007. Development was ultimately suspended, largely owing to financial considerations. “Although I believe it could work with 70–80% efficacy, it’s a difficult and expensive vaccine to make,” says Houghton. He would like to continue to develop and refine the approach in his new lab, with an eye towards future clinical trials.

The only other HCV vaccine candidates in the pipeline are from Okaïros, a Rome-based biopharmaceutical company that was spun off from drug giant Merck, that recently embarked on phase I trials with two vaccine formulations. Okaïros prophylactic strategy uses two injections — an initial ‘prime’ and a follow-up ‘boost’ — that contain distinct viral vectors, each of which expresses the same set of HCV-derived proteins. This combination approach prevents the immune response from focusing its attention on the vector at the expense of the intended target, explains Alfredo Nicosia, chief scientific officer at Okaïros. Okaïros presented initial data from one trial at this year’s International Liver Congress, in Berlin, showing that seven of ten vaccinated volunteers generated a broad T-cell response against peptides derived from a variety of HCV subtypes. This reaction was sustained over the course of a year following the prime injection, and Nicosia is optimistic that this vaccine will be ready for phase II trials later this year.

The motive for developing a prophylactic HCV vaccine is clear: to avoid the need for a toxic, unpleasant and expensive treatment that doesn’t always work. A full course of ribavirin and interferon-α costs US$25,000 in the United States. Nevertheless, there is little evidence to suggest an imminent scramble for the largely empty prophylactic marketplace.

One reason may be that the advent of potent new antiviral drugs such as telaprevir (from Vertex Pharmaceuticals, based in Cambridge, Massachusetts) and boceprevir (from Merck, based in Whitehouse Station, New Jersey) offers an efficacy of HCV treatment that removes some of the urgency from developing preventive strategies. Furthermore, because of the relatively inefficient sexual transmission of the virus, most new cases of HCV arise from unsanitary medical practices in the developing world or among injection drug users; the limited financial resources of this target population could be a serious deterrent to companies that might otherwise consider embarking on the expensive and risky journey of vaccine development. Under these conditions, commercial success might depend on the willingness of health regulatory agencies to integrate HCV prevention into the standard vaccination arsenal. Houghton sees it as an open question whether those agencies would recommend a universal HCV vaccine for adolescents, “knowing that it’s mainly the product of high-risk behaviours like intravenous drug use.”

Even if a vaccine manages to clear those hurdles, navigating through the testing process will be more tricky than usual. HCV is so good at evading the innate immune system that a successful prophylactic vaccine might not prevent acute infection, although, by bolstering adaptive immunity, the vaccine should prevent a chronic infection and subsequent reinfection. This risk of acute infection will add an ethical complication to clinical trials involving prophylactic treatment of patients in high-risk groups. Doctors who monitor these trials would be obliged to warn people who develop an acute infection and offer them prompt access to treatment, directly confounding the study results.

These challenges are not insurmountable and, as a positive example, Houghton points to the vaccine against hepatitis B virus, which also disproportionately affects injection-drug users. He adds that the expertise of investigators at agencies such as the National Institute on Drug Abuse, in Bethesda, Maryland, has been invaluable in HCV vaccine trial planning and recruitment. However, it is important to manage expectations: even a successful vaccine will probably achieve only an efficacy of 70–80% because of HCV’s remarkable escape artistry. “It’s a race between the vaccine-induced immune response and the virus,” says Nicosia, “and we need to tilt it in favour of the former in order to achieve prevention.”

Michael Eisenstein is a journalist based in Philadelphia, Pennsylvania.

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The scourge of the hepatitis C virus in the United States is woefully underestimated. Brian R. Edlin reckons it’s time the infection is given the priority it demands.

At least five million people in the United States have been infected with the hepatitis C virus (HCV)\(^1\). That’s about five times as many people as are infected with HIV. A sound public-health response to the HCV epidemic requires urgent investment in prevention, testing, treatment and research — investments that were made for HIV — to avert greater financial costs and loss of life. Indeed, a January 2010 report by the Institute of Medicine (IOM), part of the US National Academy of Sciences, warned that viral hepatitis will remain out of control unless adequate resources are devoted to prevention, control and surveillance\(^2\).

This is not the response that we are witnessing. The US government has all but ignored the threat of HCV and is under-funding prevention, treatment and research into the disease (see ‘US Response to the HIV and viral hepatitis epidemics’). The Action Plan to Prevent, Care and Treat Viral Hepatitis, which was released in May 2011 by the US Department of Health and Human Services in response to the IOM report, does not include an intention to increase funding for viral hepatitis.

Control of any epidemic starts with an accurate understanding of the magnitude of the problem, but the scope of the HCV epidemic in the United States is poorly understood. For example, the Centers for Disease Control and Prevention (CDC) estimate of the prevalence of HCV infection in the United States is four million people\(^3\). But this relies on data from a national household survey that has long been known to suffer from non-response bias and to exclude high-risk populations such as homeless people and prisoners. This survey underestimated\(^4\) the prevalence of HIV infection in the United States by a factor of 1.4 to 2.0. If the HCV estimate is similarly biased, then 6–8 million Americans are likely to have been infected with HCV.

Even less is known about the rate at which HCV is spreading. The CDC assumes that there are about 20 new infections for each case reported to its surveillance system and estimates that about 18,000 new infections occur each year — about one every 30 minutes. The actual number could be much higher. Investigators in Seattle and Baltimore, and my research teams in San Francisco and New York, have found that injection drug users, in whom most new infections in the United States occur, rarely experience symptoms when they acquire HCV — and when they do, they rarely seek medical attention\(^5\). Probably fewer than 1 in 100 new infections in injection drug users, and possibly considerably fewer, are reported to health departments. Infections in this entire group of people are thus almost invisible. What’s more, the recent explosion of opioid use among young adults has created a new silent HCV epidemic. In Massachusetts alone, more than 1,000 new HCV infections among 15–25 year olds annually since 2007 have been linked to this recent wave of drug use\(^6\).

The CDC’s surveillance system covers people who are not homeless or institutionalized, have nothing to fear from the authorities, have access to health care, feel ill when they contract HCV infection and visit a doctor when they feel ill. But HCV disproportionately affects groups for whom those attributes often don’t hold true (see ‘Hepatitis C is a disease of the marginalized’).

Even if the extent of the epidemic is unclear, basic prevention strategies could still be implemented. Prevention is the cornerstone of disease control, so the lack of funding in this area is especially troubling. Some have argued that HCV infection cannot be prevented. But there is strong evidence that the interventions that decreased HIV transmission among drug users — community-based outreach and education, testing and counselling, access to sterile syringes and substance-use treatment — also markedly reduced HCV transmission\(^7\). Once drug users learned about how HIV was spread, and barriers to obtaining sterile injection equipment were lowered, users eagerly adopted safer injection techniques, and both HIV and HCV incidence rates fell by as much as an order of magnitude from the late 1980s to the late 1990s.

HCV transmission rates were, however, far higher than those for HIV to begin with, and they remain unacceptably high. But HCV incidence rates in injection drug users fell from 15–20% per month in the 1980s to 10–25% per year after HIV prevention interventions were introduced. The median time between the first use of injection drugs and HCV infection rose from 3–4 months in the 1980s to 4–7 years in the late 1990s.

Liver disease rates will continue to rise, and about 150,000 Americans will die from viral hepatitis in the next decade.
PLAN OF ACTION

Confronting the epidemic

PREVENTION: Provide needle-exchange facilities, syringe access, community-based outreach and education, community-based services, testing and counselling, links to care and substance-use treatment to all those in need.

TESTING: Provide hepatitis C testing to populations with an elevated prevalence and wherever HIV testing is available.

CARE: Provide multidisciplinary services, comprehensive and continuing primary and specialty medical care, substance-abuse treatment, mental healthcare, case management, support services, and provider education and training nationally to all those in need.

PRISONS: Provide HCV prevention, testing and treatment services in correctional institutions.

SURVEILLANCE: Develop and implement surveillance systems for those currently overlooked by current systems.

RESEARCH: Prioritize the development of better interventions so that prevention, testing and care can be more effectively and efficiently provided to those who need it.

Hepatitis C is a disease of the marginalized

Hepatitis C disproportionately affects groups who are under-represented in health surveillance systems and underserved by the healthcare system. Percentage of each group testing positive for HCV infection.

1. Injection drug users > 10 yrs of use
2. Injection drug users < 10 yrs of use
3. Homeless persons
4. Prisoners
5. Severely mentally ill people
6. Hospital patients
7. African-American men 50–59 yrs
8. US population

1990s, opening a window of opportunity in which to slow the spread of the virus. But effective preventive interventions are not available in many locations and are poorly funded where they do exist. And research on new interventions to reduce transmission further, which is urgently needed, is not a priority at the National Institutes of Health (NIH).

About half of all HCV infections can be cured with a single 6–12-month course of therapy. Moreover, public-health programmes stop at the doors of most correctional facilities, abandoning the infected and those at risk at the moment when providing prevention and treatment services would be most practical. In 2009, the IOM put the development of better treatment strategies for at-risk populations such as injection drug users on its list of the nation’s top research priorities — but the NIH has yet to respond to the call. As a result, liver disease rates will continue to rise, and about 150,000 Americans will die from viral hepatitis in the next decade.

Public and private healthcare expenditure on hepatitis C, which is estimated at US$30 billion today, is expected to exceed US$80 billion, with an increasing proportion of the cost falling to public sources. If we fail to act now, these expenses will overwhelm our already overburdened public healthcare system.

The United States launched a vibrant response to the HIV/AIDS epidemic and made great advances in surveillance, prevention, care and treatment by investing in research and services in these areas. A timely, proportionate response to HCV will require leadership and resources. Nothing less will mitigate the extraordinary toll that viral hepatitis will take on the public’s health and on the healthcare system.

Brian R. Edlin is a professor of medicine at the State University of New York Downstate College of Medicine in New York. e-mail: brian.edlin@downstate.edu

A testing journey

Results ready in minutes and more efficacious drugs will help find and treat the hundreds of millions of carriers.

BY SARAH DEWEERDT

Obtaining an accurate diagnosis of hepatitis C often means travelling a long road, with many stops along the way. First, you’ll need a blood test to check for antibodies to the hepatitis C virus (HCV), an analysis that can take as long as two weeks. But even with antibodies, you might not be infected: 15–25% of exposed people clear the virus without needing any treatment.

The next step is to determine whether you have an active infection, and that means another blood draw to test for the presence of viral RNA — and another week or two of waiting for results. If that test comes back positive, you may need additional blood tests to determine your genotype (see ‘Playing the odds’) and the genotype of the virus, both of which affect how you are likely to respond to treatment.

This drawn-out journey is only part of the problem. HCV infection is often ‘silent’, with symptoms not developing for twenty years or more. Consequently, many infected people are unaware they have hepatitis C and never seek medical help. Estimates are that fewer than half of the people who are chronically infected know they have HCV. For some, this will not be a problem as the disease will not progress; for others it could be fatal.

Scientists and public-health advocates are now turning their attention to developing tests that are faster, cheaper and less invasive. They are also considering how to design screening programmes to identify people who might, unknowingly, be harbouring the virus. “It doesn’t matter how good your treatments are if the majority of your affected population is not diagnosed,” says Gregory Dore, head of the Viral Hepatitis Clinical Research Program at the University of New South Wales in Sydney, Australia. The good news is that hepatitis C can often be treated. And as improved medications with greater efficacy and shorter treatment times reach the market, there is a greater imperative to find and treat the people who are infected.

QUICK AND CHEAP

Several companies have rapid antibody tests for HCV in the pipeline. The first one to hit the market was developed by OraSure Technologies, a biotechnology firm in Bethlehem, Pennsylvania. The company’s OraQuick HCV Rapid Antibody Test was approved for use in Europe at the end of 2009 and in the United States in mid-2010, and is gradually being rolled out in these regions.

In the United States, the OraQuick test can be carried out with blood from a finger prick. In Europe, the less invasive method of taking a mouth swab for saliva has also been approved. Either way, a health professional places the sample into a vial and inserts a plastic strip that looks like a home pregnancy test: two red-purple lines means that the patient has antibodies to HCV. The results are ready in 20 minutes.

“We believe it’s going to dramatically expand testing opportunities,” says Stephen Lee, OraSure’s chief science officer. “Testing will be able to go on in a broad range of settings — doctors’ offices, community outreach centres, needle-exchange clinics, even mobile testing vans.” Similar rapid tests have greatly increased HIV screening and diagnosis over the last decade.

The next step in the diagnostic journey, testing for viral RNA, typically involves a method such as the polymerase chain reaction (PCR) to amplify the virus’s genetic material to a detectable level. This step is time-consuming and expensive — much of the reason why antibody testing is usually carried out first. “One of the big issues is making RNA testing affordable,” says John Ward, director of the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Faster RNA testing, he says, would also be “a fantastic development”.

One approach to improving RNA testing comes from a team led by Hassan Azzazy, a chemist at the American University in Cairo. “We are going directly to detecting HCV RNA in a single reaction, without amplifying the RNA of the virus,” he says.

Azzazy’s test uses tiny particles of gold, each about 15 nanometres in diameter. Gold nanoparticles have an unusual optical property known as ‘surface plasmon resonance’: when the particles are distributed evenly throughout a liquid, they reflect light in a way that makes them appear red; however, when they clump together, they look blue.

To perform the test, Azzazy first takes serum he adds short pieces of DNA that are
complementary to HCV RNA. The gold nanoparticles are then added to this solution. In the absence of HCV RNA, the primers stick to the gold nanoparticles and separate them — and the solution appears red. If the virus is present, the primers pair with the viral RNA instead and the gold nanoparticles aggregate, turning the solution blue (see ‘Red light, blue light’). The reaction can be carried out in a test tube, and the whole process takes about 30 minutes. “We don’t need fancy infrastructure to run the test or to interpret the results,” Azzazy says. It should cost about one-seventh as much as the current HCV RNA tests, he says, and could make antibody testing unnecessary.

**ONE-STOP TEST**
Researchers at Brazil’s Carlos Chagas Institute, part of the Oswaldo Cruz Foundation in Rio de Janeiro, aim to streamline the diagnostic process even further. Marco Krieger and colleagues say that a single RNA test could suffice both to diagnose HCV infection and to identify which subtype of the virus is present, which will help guide treatment.

There are at least six genotypes of HCV, most of which have several subtypes. In Brazil, subtypes 1a, 1b, 2a, 2b, 2c and 3a account for nearly all HCV infections. Because different genotypes are present in different parts of the world, a diagnostic test designed for one country might not work in another, says Marco Krieger, who is leading the project.

His group’s test makes use of a technology called a liquid microarray, in which short pieces of DNA are attached to tiny plastic beads, or microspheres, floating in a sample. It’s similar to a gene chip in that it can detect many nucleic acid sequences simultaneously, which makes the test both rapid and flexible.

Currently, the test is designed to identify both genetic sequences that are common to most viral subtypes, and variable sequences that distinguish between the subtypes. Unlike current RNA tests, the method can detect many different sequences in a single reaction, and Krieger says that it could easily be adapted to detect a different set of genotypes.

“The assay flexibility also allows us to add new sequences in the future, for instance, sequences related to drug resistance if necessary,” he says.

**SCREENING SELECTION**
As more diagnostic technologies are developed, other issues arise. Ward points out the need for standards to ensure that results of different tests can be compared. The CDC has begun discussions with the World Health Organization about collaborating to create such guidelines.

Another equally important issue is how to apply the tests. In the United States and many other developed countries, where the overall prevalence of HCV infection is low, mass screening isn’t cost effective. The CDC’s current HCV screening recommendations, developed in the late 1990s, advise testing those known to have been at risk of exposure to the virus. But many people who contracted the virus several decades ago, perhaps through a blood transfusion or youthful experimentation with drugs, don’t realize they are at risk and do not come forward to be tested.

According to researchers at the Amsterdam Public Health Service, the Internet could be used to find these people and help them. A team led by Maria Prins designed and validated an online screening questionnaire about risk factors such as former injection drug use, blood transfusions before blood bank screening began and immigration from countries with a high prevalence of HCV infection.

A mass media campaign including television and Internet advertisements brought almost 41,000 people to the website (www.heptest.nl), and 9,653 completed the questionnaire. Of the 1,480 people who were found to be at risk and eligible for a free blood test, 420 — nearly 30% — were tested. Prins was encouraged by this participation rate; in a similar effort aimed at syphilis, only 10% of those identified as at risk followed through and had a test, she says.

Study participants said they liked the convenience and anonymity offered by the online process. The biggest hurdle was encouraging people to take the questionnaire in the first place. “People don’t see hepatitis C as something very threatening, and they confuse it with hepatitis B,” says Prins. “They think they have already been vaccinated.” In the future, the team may combine screening efforts for the hepatitis B virus and HCV.

To avoid a looming crisis, however, public health authorities will need to cast a wider net and not wait for people to seek out a test. In particular, it makes sense to target certain age groups. In developed countries, the peak of HCV transmission was between the 1960s and 1980s. Many of those infected during this period will soon begin to develop liver damage and possibly cancer: in the United States, as many as 1 in 33 baby boomers might be infected. According to a computer model designed by a team led by Lisa McGarry of i3 Innovus, part of the health-care information technology company Ingenix, in Medford, Massachusetts, screening everyone born between 1945 and 1970 would mean carrying out more than 80 million tests in the United States alone — but it could prevent 50,000 deaths. In fact, new CDC guidelines due to be released in 2012, might include a similar recommendation for age-based screening for HCV.

“A routine test in that age group is what you want,” says Eugene Schiff, director of the Center for Liver Diseases at the University of Miami in Florida. He argues that this greatly expanded screening is key to making the journey to diagnosis shorter — and the burden of hepatitis C lower. “You’re not going to get it done otherwise.”

Sarah DeWeerd is a science writer in Seattle, Washington.