Hepatitis C can be cured globally, but at what cost?

Andrew Hill and Graham Cooke

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MEDICINE

Hepatitis C can be cured globally, but at what cost?

New drugs to cure hepatitis C should be made available at low costs in developing countries

By **Andrew Hill**[1] *and* **Graham Cooke**[2]

Worldwide, an estimated 185 million people have been infected with the hepatitis C virus (HCV). Untreated, the infection can lead to cirrhosis, liver failure, and liver cancer, causing up to 500,000 related deaths per year (*1*, *2*), and killing more people than tuberculosis or malaria (*3*, *4*). New treatments are available that can cure over 90% of people with HCV within 12 weeks (*5*). So what is the problem?

The "new generation" of drugs for HCV that are now available in the United States cost $84,000 (sofosbuvir) and $66,000 (simeprevir) per person, for a 12-week course of treatment (*6*) (see the figure). Even newer drugs are undergoing regulatory review (daclatasvir and "3D"). However, these treatments could be manufactured for as little as $78 to $166 per person for a 12-week course of two drugs, according to our recent analysis (*5*). Efforts have begun by the manufacturer to make sofosbuvir affordable in some low-income countries like Egypt ($1000), but no country is yet able to access this drug at a cost that is close to the predicted minimum production price. No other pharmaceutical company has announced similar access prices for their treatments outside the United States and Europe.

There is no vaccine against HCV, and existing "old generation" treatments are challenging. Therapies based on the cytokine interferon and the drug ribavirin (which blocks RNA synthesis by some viruses including HCV) require a course of 24 to 48 weeks, have high rates of side effects (rash, anemia, and flu-like symptoms), and fail to cure many patients (*7*). Moreover, different viral genotypes require different choice and durations of therapy. Despite these challenges, there is good news. The more recent drugs can cure the majority of people with HCV, with much improved side-effect profiles and simple oral dosing (*5*). Data are expected to show greatly improved "pan-genotypic" activity of the newer drugs. But the cost and affordability of treatment remain the biggest barrier to scaling up treatment.

As long as U.S. patents for new hepatitis C drugs are enforced, high prices will continue to restrict access to treatment. The patents on simeprevir, daclatasvir, and sofosbuvir expire in 2026, 2027, and 2029, respectively (*8*–*10*). Companies can only start production of generic versions 12 to 15 years from now, when an estimated 6 to 7.5 million more people will have died from hepatitis C if untreated, given current death rates and given that the epidemic would continue to grow.

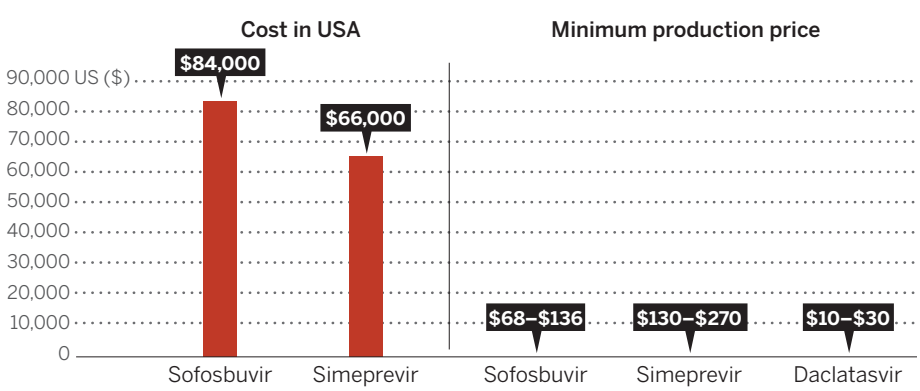
Over the past 15 years, licensing to manufacturers of generics, economies of scale, and improvements in manufacturing processes have driven the cost of antiretroviral (ARV) treatment for HIV infection down by more than 99%, with standard HIV treatment now costing as little as $60 per patient per year, using the same standard of care that patients receive in the richest nations (*11*). This price could not have been imagined when effective HIV treatment was introduced at over $10,000 per patient per year in the late 1990s (*12*). Universal access to treatment for HIV/AIDS in developing countries was initially considered too complex and expensive to be feasible. With the invention of a simple and effective therapy (ARVs), a competitive market was created for companies to mass produce generics, which, in turn, lowered costs and made treatment affordable. Along with associated international funding, treatment scale-up became possible (*12*). There are now more than 10 million people receiving treatment for HIV in poor countries, at a very low price.

Similar innovation and progress is possible for hepatitis C treatment. There is no reason to predict that the new generation of HCV drugs should be particularly expensive to manufacture. For example, one of the most promising early combination treatments for hepatitis C—sofosbuvir and daclatasvir—cured over 90% of patients after 12 weeks (*13*). A 12-week course of these drugs could be manufactured for between $78 and $166 per person if the same methods of mass-producing generic drugs for HIV/AIDS are applied (*5*). But who will pay for the treatments (even at reduced prices) and the related costs of screening, diagnosis, and care? The current high prices of new hepatitis C treatments will place a strain on all healthcare systems. In the United States, Congress is investigating the pricing of sofosbuvir, including the methods used to establish the cost. In the United Kingdom, national reimbursement authorities may not recommend payment for sofosbuvir.

Of the 20 countries with the largest HCV epidemics, 12 are classified as low or lower-middle income (*5*). In many of the poorest countries, there are few or no programs to treat HCV, so new funding streams are needed to support the scale-up of treatment as part of comprehensive control and prevention programs. Such funding needs to be matched with commitments from pharmaceutical companies in wealthy nations so that new-generation drugs can be made at minimal cost. Thus, pharmaceutical companies should allow generic companies to

Costs of new drugs for hepatitis C per person, 12-week course

New generation drugs for HCV



[1]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3BX, UK. [2]Imperial College London, London SW7 2AZ, UK. E-mail: microhaart@aol.com

mass produce these treatments for use in low-income countries at a cost close to the cost of production, with a small royalty paid back to the pharmaceutical companies. This is the same mechanism used to sell vaccines in low-income countries. In some countries, reductions in the price of HIV-1 treatments were only achieved after long legal battles with pharmaceutical companies. In some cases, countries overruled company patents on drugs and started importing generic drugs at lower costs—so-called compulsory licensing—which is permitted in cases of national medical emergencies.

Creating a new funding mechanism for poor nations is difficult in the current economic climate, but HIV has left a legacy of structures ready to adapt to hepatitis C to complement government and private-sector efforts. UNITAID, the United Nations agency created in 2006 to overcome market barriers for treatments of HIV, tuberculosis, and malaria, recently announced its first funding for hepatitis C, with an aim of reducing treatment costs to $500 to $1000 per patient (*14*). It plans to scale up treatment through a multinational group of HIV programs run by Médicins Sans Frontières, the international medical humanitarian organization. The Global Fund, which addresses HIV/AIDS, tuberculosis, and malaria, has funded treatment programs with old-generation HCV drugs in several developing countries for the past 3 years.

If we can learn from the lessons of HIV/AIDS, mass production of generics can save millions of lives. This has been an inspiring medical success story which need not stand alone but can be repeated, even more rapidly, for hepatitis C. ■

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BIOCHEMISTRY

Fishing for peroxidase protons

Where are the protons in heme protein catalysis?

By **John T. Groves** *and* **Nicholas C. Boaz**

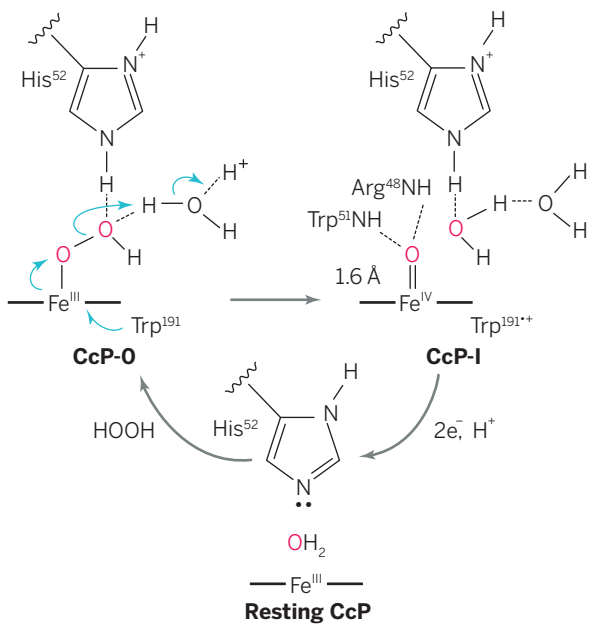
Cytochrome c peroxidase (CcP) consumes hydrogen peroxide in mitochondria, using electrons derived from reduced cytochrome c. This and a related enzyme, horseradish peroxidase (HRP), have played key roles in the development of structural and mechanistic biochemistry and are used in biocatalysis and chemiluminescent bioassays (*1*). On page 193 of this issue, Casadei *et al.* (*2*) use neutron diffraction to reveal the role and origin of protons in heme oxidation by hydrogen peroxide, a key step in this essential enzymatic reaction.

CcP and HRP were the first heme enzymes for which oxidized intermediates were observed (*1*). In the textbook mechanism for heme oxidation, protonated histidine N-H assists O-O bond heterolysis in an Fe(III)-OOH intermediate (CcP-0), producing CcP compound I (CcP-I) and water. The overall course of this reaction was established long ago. But where are the protons? Casadei *et al.* use neutron diffraction to reveal the positions of protons in resting CcP and CcP-I. They show that the iron(IV) of CcP-I is an unprotonated ferryl, Fe(IV)=O. The results bring new clarity to heme oxidation by hydrogen peroxide (see the figure).

Neutron diffraction has distinct advantages over x-ray diffraction techniques for the structural characterization of enzymes that contain redox-active metals. Non-ionizing neutron beams avoid the photoreduction that often plagues structural analysis with x-rays and that also occurs in the laser beams used for resonance Raman spectroscopy. Laser and x-radiation lead to ambiguities in the oxidation states of redox-active metals such as iron or manganese. By contrast, neutrons interact only with atomic nuclei and scatter much more effectively from hydrogen and, especially, deuterium atoms. Catalytic proton networks and even deuterated hydronium ions (D_3O^+) have been observed in proteins by means of neutron diffraction (*3*, *4*).

Efforts to understand the atomic and electronic structure of the oxidized intermediates in the CcP catalytic cycle have been hampered by the fact that Fe(III)/Fe(IV) redox potentials in heme proteins lie in the same range as those of the porphyrin ring and those of tryptophan and tyrosine. This "redox non-innocence" greatly increases the complexity of these systems because it increases the number of plausible sites of oxidation. In HRP-I and in model porphyrin complexes, ferryl states, Fe(IV)=O, with very short Fe-O bond lengths have been reported (*5*, *6*). The distinction between Fe(IV)=O species and their hydroxylated equivalents, Fe(IV)-OH, has taken on considerable importance with recent evidence that cytochrome P450 compound II is protonated and that the basicity of ferryl oxygen strongly affects heme protein reactivity (*7*).

To identify the positions of active-site protons in CcP and CcP-I, Casadei *et al.*



Proton-mediated mechanism. Reaction of ferric CcP with H_2O_2 first gives CcP-0, followed by O-O bond scission driven by external protonation to afford CcP-I. Casadei *et al.* now report neutron diffraction data that pinpoint the locations of the protons and elucidate the catalytic mechanism.

Department of Chemistry, Princeton University, Princeton, NJ 08544, USA. E-mail: jtgroves@princeton.edu