PHARMACEUTICALS

Advocates Protest the Cost of a Hepatitis C Cure

For disease advocates, the U.S. Food and Drug Administration's 6 December approval of what promises to become a blockbuster drug against the hepatitis C virus (HCV) was bittersweet news. Sofosbuvir, made by Gilead Sciences of Foster City, California, works better than anything on the market: It's effective against most HCV variants and will help rid the body of this liver-damaging virus more quickly and safely than existing drugs. What rankles advocates is its price—each pill costs $1000, and the drug must be used for at least 12 weeks—which will put it out of reach of most of the more than 100 million people in resource-limited countries who need it. "It doesn't matter how great these drugs are if no one can have them," says Tracy Swan, who works with the Treatment Action Group, a New York City nonprofit whose members successfully battled big pharma as leading AIDS activists in ACT UP.

In an unusual move, Swan and other HCV advocates have been imploring Gilead to offer a lower price to cash-strapped countries right from the start. They want to avoid a repeat of what happened during the early days of the AIDS epidemic, when it took years—and many protests and lawsuits—before the poor had access to lifesaving antiretroviral drugs. "We want the drug now—not in 15 years," says Isabelle Meyer-Andrieux, a clinician based in Geneva, Switzerland, who works for the Campaign for Access to Essential Medicines run by Doctors Without Borders (Médecins Sans Frontières [MSF]). "We are really convinced that this drug can revolutionize the way we treat HCV in low- and middle-income countries."

Meyer-Andrieux says that Gilead seems receptive to differential pricing, a strategy the company uses for its anti-HIV drugs. Gregg Alton, Gilead's executive vice president for corporate and medical affairs, wrote in an e-mail to *Science* that the company hopes "to develop an appropriate access and pricing strategy" and "greatly values" input from advocates. "Providing treatment in resource-limited settings presents complex challenges and we understand the concerns that have been raised," he wrote.

HCV, which can cause life-threatening cirrhosis and liver cancer, infects an estimated 130 million to 185 million people—and 90% of them live in poorer countries (see map). It's mainly transmitted through contaminated blood transfusions or syringes shared by injecting drug users, but sexual transmission can occur, too. There are six main viral variants, called genotypes, which respond differently to treatments. New drugs are desperately needed.

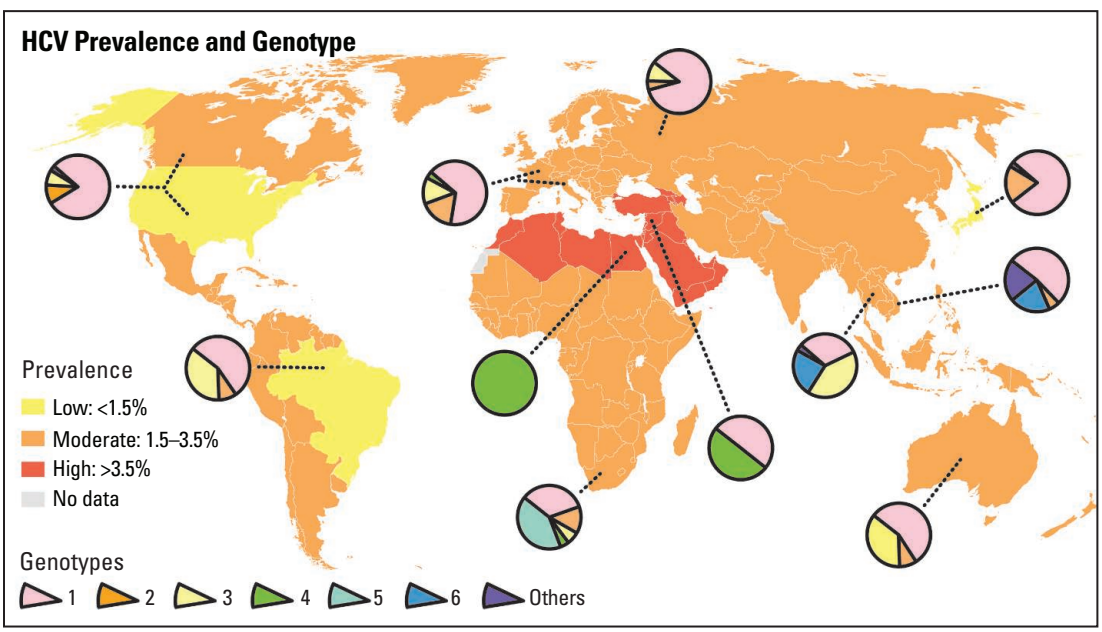
Until 2011, the only treatment was an unpopular 48-week regimen that combined injections of interferon with ribavirin pills, which boosted the immune system and had some nonspecific antiviral effect but didn't directly attack HCV. The treatment often had severe side effects and cured fewer than 50% of those with genotype 1, which infects about 70% of the estimated 3 million people in the United States with hepatitis C. In the past 3 years, three drugs have come to market that directly attack HCV and reduce treatment regimens to 12 to 28 weeks, but they are approved only to treat genotype 1, some have serious side effects, and cure rates are, at best, 80%.

Gilead's sofosbuvir cripples an HCV enzyme, polymerase, that the virus needs to copy itself. The drug cures roughly 90% of genotype 1, 2, and 4 infections in 12 weeks with relatively minor side effects, when given with ribavirin and, for genotypes 1 and 4, interferon injections. It's also approved for use in combination with ribavirin for genotype 3, although efficacy is slightly lower and treatment takes 24 weeks.

The drug's performance in early studies led Gilead in January 2012 to pay a staggering $11.2 billion to purchase the small company that first made it. But Meyer-Andrieux argues that the full-price sales of the drug in wealthy countries will offer the company ample profit. "They don't have to treat so many patients to reimburse the $11 billion," she says. A 20 November investor report from Credit Suisse bank, subtitled "The HCV Revolution," suggests sofosbuvir's sales in wealthy countries in 2014 alone could total $3 billion.

"The drugs are extremely cheap to make," contends Andrew Hill, a pharmacologist at the University of Liverpool in the United Kingdom. Based on the raw ingredients, the steps in the chemical synthesis, and molecular similarities to anti-HIV drugs, Hill and his colleagues concluded that it costs $68 to $136 to manufacture enough sofosbuvir to treat a person for 12 weeks. MSF suggests that diagnosing and curing an HCV infection should cost developing countries no more than $500.

Hoping to pave the way for an inexpensive generic version of sofosbuvir, another nonprofit is challenging Gilead over its Indian



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patent application, a strategy that also proved successful with anti-HIV drugs. The Initiative for Medicines, Access & Knowledge (I-MAK) in New York City filed an "opposition" to the Indian sofosbuvir patent application on 21 November, contending that sofosbuvir is a slight variation on an earlier patented drug that had activity against HCV and thus is not novel. Gilead did not respond to *Science*'s question about the I-MAK opposition.

Many expect that sofosbuvir will prove even more powerful when combined with one of several other anti-HCV drugs in late-stage development. Meyer-Andrieux of MSF says the group is also trying to establish differential pricing for those drugs, and ultimately hopes to convince companies to coformulate one pill that works against all genotypes. "We would very much like to take the best drugs and combine them and escape from big pharma monopoly strategies," Meyer-Andrieux says.

When a short course of pills can cure all HCV infections, demand for treatment will intensify further, says David Thomas, who treats hepatitis C at Johns Hopkins University in Baltimore, Maryland. Says Thomas: "I can't imagine anyone who won't want the cure."

–JON COHEN

ANCIENT DNA

Fossilized Teeth Offer Mouthful on Ancient Microbiome

LONDON—In pretoothbrush populations, a thick, visible crust of calcium phosphate, food particles, and trapped microorganisms often marred gumlines. Dental calculus, or tartar, still plagues many, and dentists attack it with metal picks and abrasives. "It's a meandering line of caramel-colored, cementlike material," says Christina Warinner, an anthropologist at the University of Oklahoma, Norman. "It's quite gross."

It can also be a treasure for those studying ancient DNA. At a recent meeting here,* researchers noted that the microbial DNA preserved in ancient dental calculus—and in equally prosaic human coprolites (fossilized or preserved feces)—carries a record of the communities of bacteria that lived in and on people who died hundreds or thousands of years ago. "I think it's the biggest untapped resource in ancient DNA," says Laura Weyrich, a microbiologist at the University of Adelaide in Australia, who co-authored a paper on DNA in calculus from fossilized teeth earlier this year (*Science*, 22 February, p. 896). "We've just scratched the surface."

The microbiome, the myriad bacteria that naturally inhabit our mouths, guts, and other tissues, is increasingly recognized as a vital component of human health—and disease. Researchers want to know how thousands of years of civilization have changed this invisible ecosystem, for good or for ill, and ancient samples can offer a window on the past. "By better understanding the natural [microbiome] state, we can better understand the diseases of civilization we're struggling with today," suggests Cecil Lewis, a molecular anthropologist at the University of Oklahoma, Norman.

They already have some tantalizing results. At the meeting, Warinner noted that her studies of calculus from ancient humans show that genes associated with resistance to the antibiotic tetracycline, widespread in modern samples, were once scarce. And earlier this year, Lewis reported that 1400-year-old ancient coprolites found at a site in Mexico yielded DNA from spirochetes, a kind of bacteria not found in most modern human guts—but present in remote, rural populations recently studied in Africa and South America. "We have this spirochete found on two separate continents, with the commonality being rural populations—one of them from 1400 years ago," Lewis says. "Now we can ask, 'Why is it there?' "

CREDIT: CHRISTINA WARINNER

Tooth pick. A researcher looking for ancient DNA samples dental calculus from a 1000-year-old tooth found in Peru.

Well-preserved human coprolites are rare and prone to contamination. Calculus, on the other hand, is nearly ubiquitous on ancient human teeth. Researchers hope to dissect its fine layers to see how the microbiome changes over an individual's lifetime, but it is so rich in genes that they can be overwhelmed. "In some samples, the DNA concentration in ancient dental calculus is as high as in fresh human liver," Warinner says. To deal with the surfeit of biological material, she and Lewis are building a special "high-biomass" ancient DNA lab at Oklahoma.

As always in ancient DNA, contamination is a worry. Studying ancient dental calculus is "a good approach, but it's not bulletproof," says veteran ancient DNA researcher Eske Willerslev of the University of Copenhagen.

To sort environmental microbes from original inhabitants of the calculus, Weyrich "fries" fossilized samples under ultraviolet light for 15 minutes, then soaks them in bleach for another 5 to kill anything on the outside. The samples are then pulverized under sterile conditions and sequenced. Researchers can also match the DNA of microorganisms they find in ancient samples with libraries of sequences of known microbial communities, such as the gut microbiome. "If you compare it to soil and water and the sample still looks gutlike, that's a good sign," Lewis says.

At her talk in London, Warinner also described comparing microorganisms from the inner dentin of a fossilized tooth, which is open to the environment after death, to those from the crust of preserved plaque just a few millimeters away. "They're quite distinct," Warinner said. Dental calculus "samples greatly resemble human oral microbiome samples … whereas our dentin sample resembles things like ground water, soil, and leaf litter."

Until now, archaeologists and conservators often removed calculus to better study a human skeleton's teeth, and simply discarded it. "It was always the thing that got in the way," says Amanda Henry of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. She hopes they'll now put away their dental picks. "We had no idea how informative it could be."

–ANDREW CURRY

*Ancient DNA: the first three decades, Royal Society, London, 18–19 November.