BILL HACKWELL

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

PERSPECTIVE

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 trails.

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[4-6], 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[1-3]. 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 decompensated, 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 to terms with 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. ■

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