Review

Highly active anti-hepatitis C therapy: seven lessons from HIV

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The HCV direct-acting antiviral treatment era is underway. Although there are some important differences, it is likely that the experience with HCV will be similar in many respects to what already occurred with HIV. This paper considers seven important lessons learned with HIV and the degree to which they should be anticipated with HCV.

Lesson 1. Treatment saves lives

It is possible that HIV treatment is the most important medical advancement of the past 3 decades. The widespread use of antiretroviral therapy in the mid-1990s had an immediate effect on HIV-related mortality. By 1995, the number of individuals dying of HIV-related causes exceeded 50,000 per year in the US alone (Figure 1). Given the incubation of the virus, HIV-related mortality was projected to continue to increase throughout the decade. However, by 2000, fewer than 20,000 individuals were reported to have died of HIV-related causes in the US. Similar patterns were seen in Europe and Australia; wherever antiretroviral therapy use was widespread, HIV mortality declined. One report estimated that ≥3 million years of life were saved by antiretroviral therapy up to 2003 in the US alone [1]. A pharmaceutical breakthrough had an enormous mortality effect at the population level. Considering the young ages of those who might have died, the number of life-years saved puts antiretroviral therapy on par with any other medical breakthrough.

HCV treatment can also save lives. In 2007, HCV infection killed more people in the US than HIV [2]. Just as HIV-related mortality was supposed to increase in the 1990s, HCV-related mortality is also projected to climb. At least a doubling of HCV-related cirrhosis is predicted by 2020 (Figure 2) [3]. There is evidence that effective treatment of HCV can reduce HCV-related mortality. Veldt et al. [4] showed that individuals who achieved a sustained virological response to pegylated interferon and ribavirin had a 79% reduction in the incidence of liver failure, hepatocellular carcinoma or death, compared with those who failed to respond to treatment. In a similar study of HIV–HCV-coinfected individuals, Berenguer et al. [5] also showed over a mean follow-up of 20.8 months that incidence rates per 100 person-years of overall mortality, liver-related mortality and liver decompensation were, respectively, 0.46, 0.23 and 0.23 among patients with sustained virological response and 3.12, 1.65 and 4.33 among those without sustained virological response. No doubt those who responded to treatment also are those who had lower pretreatment disease stage. However, notably, the reductions in disease complications continue years after treatment and the differences in incidence increase. Thus, as treatment efficacy improves, anti-HCV therapy has the potential to rival the clinical benefits seen with antiretroviral therapy.

Lesson 2. Reap what you sow: the public health effect of treatment is as significant as the investment

By 2000, when antiretroviral therapy had obviously markedly reduced the effect of HIV in the US, Europe and Australia, HIV-related mortality in Africa was still increasing. It was not that individuals in Africa had different antiretroviral therapy, they had no antiretroviral therapy. Some were concerned that poor individuals without adequate public health infrastructure would not be able to take antiretroviral therapy. There were worries about adherence and medical monitoring, and then there was the cost. Nonetheless, through the Global Fund and US Presidential Emergency Program for AIDS Relief, billions of US dollars were appropriated for AIDS care. The effective antiretroviral therapy treatment era in sub-Saharan Africa is now well underway. The World
Figure 1. AIDS diagnoses, deaths and persons living with AIDS, 1985–2008 US and dependent areas

Reproduced from the CDC website [28]. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Death may be due to any cause.

Figure 2. Stacked prevalence curves showing number of cases by year with cirrhosis according to gender and age at time of initial HCV infection

Health Organization estimates that, by the end of 2010, 6.6 million individuals in low- and middle-income countries were on antiretroviral therapy.

Antiretroviral therapy was just as effective in sub-Saharan Africa as in wealthy nations. Whether in Haiti or Uganda, multiple studies documented the effective suppression of HIV, dispelling misconceptions that drugs could not be taken reliably by the poor [6,7]. With appropriate counselling and patient buy-in, medications can be taken faithfully for years even by the poorest individuals. Fortunately, HCV treatment will be measured in months, not years, and the example of HIV proves treatment is possible anywhere in anyone.

Lesson 3. Pharmaceutical companies are important partners

Much of the research and development that led to antiretroviral therapy was undertaken by pharmaceutical companies. In addition, when the decision was made to make antiretroviral therapy widely available in resource-poor countries, it was crucial to have pharmaceutical cooperation on pricing and availability. In some settings they also invested millions of US dollars to create healthcare infrastructure so that appropriate research and care could be delivered.

The lesson of the early antiretroviral therapy era is that, although wealthy individuals in developed countries will receive efficacious therapies and their benefits, something extra has to be done to reach the poor. There is no question that this will be the case for HCV. Eliminating interferon injections from the treatment regimen is certainly a step in the right direction [8]. However, concerted global efforts will be needed before those treatments reach many of the 170 million individuals infected worldwide. Those efforts will have to include pharmaceutical companies. As long as HCV care costs approximately $80,000 USD, there is virtually no hope of a widespread global effect.

Lesson 4. New treatments need new models

Screening for infection is the foundation of effective treatment programmes. Enthusiasm for screening for HIV infection had been constrained by the thought that little could be done in many instances. However, not only was this nihilism dispelled by more efficacious therapy, but also it was obvious that antiretroviral therapy was both cost-effective and more medically effective when individuals were started at early disease stages (for example, CD4+ T-lymphocytes >500 cells/mm³) [9]. What followed were revised methods to screen for HIV infection [10]. The mantra was ‘seek, test and treat’, reflecting the urgency to identify HIV-infected individuals and get them into care, if not treatment. Eventually, in the US, for example, it was recommended that everyone 13–64 years of age have ≥1 HIV test; currently, approximately 80% of all HIV-infected individuals have been identified [10].

Most individuals with HCV infection are not aware they have it. An estimated 60% of HCV-infected individuals in the US are unaware of their condition [11]. In some European countries like France it is better [12]. However, worldwide no more than 5% of the 170 million are aware of their infection [8]. Thus, even if a treatment were discovered that was 100% efficacious, it could be no more than 5% effective at combating HCV in the population (Figure 3). Not unlike a drug that is 100% efficacious in vitro, but not absorbed into the body, more work is needed to develop models of HCV care that have a global effect. As with HIV, new programmes to expand testing for HCV infection have to come when there is efficacious oral therapy.

New models of care delivery will also be needed. In the very early days, HIV care was provided by an uncoordinated matrix of providers and family members. Ultimately, it became evident that multidisciplinary teams were most effective. Nurse practitioners and physician’s assistants with experience and training in HIV care were better providing that care than physicians without commensurate experience [13]. Creative models had to be developed to reach special patients, such as participants in methadone programmes and inmates, and to coordinate case finding and treatment.

Similar lessons are likely to apply to HCV care. However, because HCV can be cured with several months of antiviral treatment and HIV treatment is still a lifelong illness, the models may differ. Arora et al. [14] have already proven that HCV care can be expanded to community health centres by using innovative delivery strategies. When ‘all-oral’ treatments are available, it may be possible to treat HCV with even less health infrastructure. In fact, any model where individuals are able to be engaged in care for several months may be sufficient.

Lesson 5. There is more to the disease than the virus

Even when HIV replication was stopped with antiretroviral therapy, there remain poorly understood complications of infection. Often referred to as immune activation, individuals with HIV on effective antiretroviral therapy remain at increased risk for complications such as cardiovascular disease, some cancers and cirrhosis [15–17]. There are strong correlations between these non-AIDS outcomes and various expressions of residual immune activation, such as attenuated restoration of CD4+ T-lymphocyte populations, enrichment of CD38+ CD8+ T-lymphocytes, elevated plasma levels of type-1 interferons and blood cytokines, and markers.
of immune senescence and/or microbial translocation such as lipopolysaccharides, soluble CD14 and lipopolysaccharide-binding protein [18–20].

It is likely that the situation will be similar as HCV-infected individuals with cirrhosis are cured. Cirrhosis is also strongly associated with microbial translocation and CD4+ T-lymphocyte depletion, even in individuals without HIV infection [21,22]. The extent to which many HCV-related conditions will be reversed by cure is not really known. Although the incidences of death and liver complications are reduced by cure, the risk of hepatocellular carcinoma persists. There are also important comorbid conditions, such as illicit drug use, that can affect the quality and longevity of life and will not be directly affected by HCV treatment. Thus, as with HIV, some complications of HCV infection may remain challenges for years after effective treatment.

**Lesson 6. Antiviral drugs select for resistant virus**

A fundamental principle of antiviral therapy is antiviral resistance, and the subject of antiviral resistance has been a dominant part of the HIV field. HIV providers knew to avoid resistance by using multiple antiviral drugs with different mechanisms of action. When resistance occurred, complex salvage regimens could be required to achieve antiviral suppression. Resistant viruses were transmitted, and pretreatment resistance testing became the standard of care.

Many of these lessons are likely to apply to HCV care. Resistance to HCV protease inhibitors and other direct-acting agents has already been well-characterized [23,24]. The lack of an archive of these viruses may reduce the long-term implications, compared with HIV, which integrates drug-resistant DNA into host cells. When used with pegylated interferon and ribavirin, baseline HCV protease inhibitor resistance has not been a strong predictor of response [25]. However, this is likely to change if there is baseline resistance to key elements of an all-oral direct-acting HCV treatment. Shorter treatment periods and rapid suppression on treatment might also diminish the risk that these viruses will be spread to others. In addition, the use of direct-acting drugs with high barriers to resistance, such as the nucleotide inhibitors, may be especially important.

**Lesson 7. New treatment brings new complications including drug–drug interactions**

One of the early lessons of widespread use of antiretroviral therapy was that the medications could cause serious long-term adverse effects. Serious metabolic complications including lipodystrophy, kidney stones and neuropathies occurred. Less serious side effects, such as nausea, headaches and diarrhoea were also
widespread and early regimens could involve dozens of pills taken as frequently as 5 times a day. There were also serious drug–drug interactions that made it difficult to treat other conditions. That experience ultimately led to guidelines that restricted antiretroviral therapy use to only those individuals at greatest risk of AIDS (for example, CD4+ T-lymphocyte counts <350 cells/mm³). However, new generations of medications have led to the ‘one-pill-once-a-day’ paradigm, and guidelines have accordingly called for more widespread treatment.

Providers who are already using HCV protease inhibitors with pegylated interferon and ribavirin will readily appreciate the parallels. Multiple medications with complex food requirements, drug interactions, and myriad of common side effects are the rule [26]. However, there are scores of compounds in Phase I–III clinical trials and provisional evidence that, at least in principle, some HCV infections can be cured without interferon-α injections and with substantial reductions in pill burden. Hopefully, as with HIV, there will soon be one safe pill to take once a day.

Summary

Although there are important differences, it is likely that the introduction of direct-acting HCV agents will in many ways be similar to what has already occurred with HIV. There will be new side effects, antiviral resistance, and new ways to treat patients. New CDC screening guidelines are also expected in the US that will focus on the cohort born between 1945 and 1965, who comprise more than two-thirds of HCV-infected individuals [27]. However, it remains to be seen whether the most important lesson of antiretroviral therapy will be learned. Will there be a widespread, coordinated global antiviral effort that saves millions of lives or will these exciting antiviral breakthroughs only reach 5–10% of those at risk?

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References


