Published in final edited form as:

Antivir Ther. 2012 ; 17(6 0 0): 1183–1188. doi:10.3851/IMP2429.

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

David L. Thomas, MD

Johns Hopkins School of Medicine, Suite 437 1830 Monument Street, Baltimore, MD 21205,
410-502-7134

Summary

The hepatitis C virus (HCV) direct 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 advance of the past 3 decades. The widespread use of antiretroviral therapy in the mid 1990s had immediate impact on HIV related mortality. By 1995, the number of persons dying of HIV related causes exceeded 50,000/year in the United States 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 persons were reported to die of HIV related causes in the United States. Similar patterns were seen in Europe and Australia; wherever antiretroviral therapy use was widespread, HIV mortality declined. One report estimated that at least 3 million years of life were saved by antiretroviral therapy up to 2003 in the United States alone.¹ A pharmaceutical breakthrough had enormous mortality impact at the population level. Considering the young ages of those who would 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, hepatitis C virus (HCV) infection killed more people in the United States 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 and coworkers showed that persons who achieved a sustained virologic response (SVR) to peginterferon and ribavirin had a 79% reduction in the incidence of liver failure, hepatocellular carcinoma, or death compared to those who failed to respond to treatment.⁴ In a similar study of HIV/HCV coinfecting persons, Berenguer and coworkers also showed over a mean follow-up of 20.8 months, the incidence rates per 100 person-years of overall mortality, liver-related mortality, and liver decompensation were 0.46, 0.23, and 0.23 among patients with SVR and 3.12, 1.65, and 4.33 among those without SVR.⁵ No doubt those who respond to treatment also are those who had lower pre-treatment disease stage. But, 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.*

Correspondence to: David L. Thomas.

Disclosure

Dr. Thomas has served as a scientific advisor to Merck, received funds for research from Merck, and has been provided antiretroviral therapy for a clinical trial from Merck and Gilead.

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

By 2000, when antiretroviral therapy had obviously markedly reduced the impact of HIV in the United States, Europe and Australia, HIV-related mortality in Africa was still increasing. It wasn't that they had different antiretroviral therapy; they had no antiretroviral therapy. Some were concerned that poor persons 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 United States Presidential Emergency Program For AIDS Relief, billions of dollars were appropriated for AIDS care. The effective antiretroviral therapy treatment era in sub-Saharan Africa is now well underway. The World Health Organization estimates that by the end of 2010 6.6 million persons 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 counseling and patient buy-in, medications can be taken faithfully for years even by the poorest persons. 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 critical to have pharma cooperation on pricing and availability. In some settings they also invested millions of dollars to create health care infrastructure so that appropriate research and care could be delivered.

The lesson of the early antiretroviral therapy era is that, whereas rich people 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 persons infected worldwide. Those efforts will have to include pharmaceutical companies. As long as HCV care costs ~\$80,000 USD, there is virtually no hope of widespread global impact.

Lesson 4. New treatments need new models

Screening for infection is the foundation of effective treatment programs. Enthusiasm for screening for HIV infection had been constrained by the thought that little could be done in many instances. But, 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 person were started at early disease stages (e.g., CD4+ lymphocyte >500/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 persons and get them into care, if not treatment. Eventually, in the United States for example, it was recommended that everyone 13–64 years of age have at least one HIV test; currently, approximately 80% of all HIV infected persons are have been identified.¹⁰

Most persons with HCV infection are not aware they have it. An estimated 60% of HCV infected persons in the United States 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 could be 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 global impact. As with HIV, new programs 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 physicians 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, like participants in methadone programs 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 lifelong, the models may differ. Arora and coworkers have already proven that HCV care can be expanded to community health centers by using innovative delivery strategies.¹⁴ When “all-oral” treatments are available, it may be possible to treat HCV with even less health infrastructure. In fact, any model where persons 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, persons 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+ lymphocyte populations, enrichment of CD38+ CD8+ lymphocytes, elevated plasma levels of type 1 interferons and blood cytokines, and markers of immune-senescence and/or microbial translocation such as LPS, soluble CD14 and LPS binding protein.^{18–20}

It is likely that the situation will be similar as HCV infected persons with cirrhosis are cured. Cirrhosis is also strongly associated with microbial translocation and CD4+ lymphocyte depletion, even in persons 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 impacted 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 pre-treatment resistant testing became the standard of care.

Many of these lessons are likely to apply to HCV care. Resistance to the 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 to HIV which integrates drug-resistant DNA into host cells. When used with peginterferon and ribavirin, baseline HCV protease inhibitor resistance has not been a strong predictor of response.²⁵ But, 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 like nausea, headaches and diarrhea were also widespread and early regimens could involve dozens of pills taken as much as 5 times a day. There were also serious drug-drug interaction that made it difficult to treat other conditions. That experience ultimately led to guidelines that restricted antiretroviral therapy use to only individuals at greatest risk of AIDS (e.g., CD4+ lymphocyte counts <350/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 peginterferon and ribavirin will readily appreciate the parallels. Multiple medications with complex food requirements, drug interactions, and myriads of common side effects are the rule.²⁶ However, there are scores of compounds in phase 1–3 clinical trials and provisional evidence that, at least in principle, some HCV infections can be cured without interferon alfa injections and with substantial reductions in pill burden. Hopefully, as with HIV, there will be 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 United States that will focus on the cohort born between 1945 and 1965 who comprise more than two-thirds of the HCV infected persons.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?

Acknowledgments

This work was funded in part by R01DA016028.

Reference List

1. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis.* 2006; 194:11–19. [PubMed: 16741877]
2. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012; 156:271–278. [PubMed: 22351712]
3. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010; 138:513–21. [PubMed: 19861128]
4. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med.* 2007; 147:677–684. [PubMed: 18025443]
5. Berenguer J, Alvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology.* 2009; 50:407–413. [PubMed: 19575364]
6. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med.* 2005; 353:2325–2334. [PubMed: 16319381]
7. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007; 46:187–193. [PubMed: 17693883]
8. Thomas DL. Curing hepatitis C with pills: a step toward global control. *Lancet.* 2010; 376:1441–1442. [PubMed: 20951421]
9. Bartlett JG, Branson BM, Fenton K, et al. Opt-out testing for human immunodeficiency virus in the United States: progress and challenges. *JAMA.* 2008; 300:945–951. [PubMed: 18728268]
10. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep.* 2006; 55:1–17. [PubMed: 16988643]
11. Volk ML, Tocco R, Saini S, et al. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology.* 2009
12. Lettmeier B, Muhlberger N, Schwarzer R, et al. Market uptake of new antiviral drugs for the treatment of hepatitis C. *J Hepatol.* 2008; 49:528–536. [PubMed: 18682313]
13. Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med.* 2005; 143:729–736. [PubMed: 16287794]
14. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med.* 2011; 364:2199–2207. [PubMed: 21631316]
15. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med.* 2007; 146:87–95. [PubMed: 17227932]
16. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med.* 2006; 166:1632–1641. [PubMed: 16908797]
17. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. *Ann Intern Med.* 2010; 153:452–460. [PubMed: 20921544]
18. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature Medicine.* 2006; 12:1365–1371.
19. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis.* 2010; 51:435–447. [PubMed: 20597691]
20. Fernandez S, Tanaskovic S, Helbig K, et al. CD4+ T-cell deficiency in HIV patients responding to antiretroviral therapy is associated with increased expression of interferon-stimulated genes in CD4+ T cells. *J Infect Dis.* 2011; 204:1927–1935. [PubMed: 22006994]
21. Benten D, Schulze zur WJ, Sydow K, et al. The transhepatic endotoxin gradient is present despite liver cirrhosis and is attenuated after transjugular portosystemic shunt (TIPS). *BMC Gastroenterol.* 2011; 11:107. [PubMed: 21978390]

22. Day CL, Lauer GM, Robbins GK, et al. Broad specificity of virus-specific CD4+ T-helper-cell responses in resolved hepatitis C virus infection. *J Virol.* 2002; 76:12584–12595. [PubMed: 12438584]
23. Kieffer T, Sarrazin C, Bartels D, et al. Wild-type HCVNS3 protease re-emerges during follow-up after 14 days of dosing with VX-950 in patients with genotype 1 HCV. *Journal of Hepatology.* 2006; 44:S7.
24. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology.* 2010; 138:447–462. [PubMed: 20006612]
25. Susser S, Vermehren J, Forestier N, et al. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. *J Clin Virol.* 2011; 52:321–327. [PubMed: 21924672]
26. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology.* 2011; 54:1433–1444. [PubMed: 21898493]
27. Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med.* 2012; 156:263–270. [PubMed: 22056542]

Figure 1.
AIDS Diagnoses and Deaths in the United States 1985–2008 (from www.cdc.gov/hiv/topics/surveillance)

Figure 2.
Projected increase in cirrhosis due to HCV infection in the United States, from Davis et al³

Figure 3.

Low global impact of improving HCV treatment efficacy with direct acting agents without expanding HCV testing and treatment initiation, from Thomas ⁸