What Is Killing People with Hepatitis C Virus Infection?

Jason Grebely, B.Sc., Ph.D.,1 and Gregory J. Dore, M.B.B.S., Ph.D., F.R.A.C.P., M.P.H.1

ABSTRACT

The burden of hepatitis C virus (HCV)-related morbidity and mortality continues to rise. Progression to advanced liver disease among HCV-infected individuals generally requires decades, but we are entering an era where those infected with HCV in the 1970s and 1980s are at significant risk of mortality. Liver disease has overtaken drug-related harm as the major cause of mortality in HCV-infected individuals in many settings. Direct-acting antiviral therapies have provided renewed optimism, but HCV treatment uptake will need to increase markedly to reduce liver disease mortality. This review provides updated information on the natural history of HCV, disease-specific causes of mortality among people with HCV, estimates and projections of HCV-related disease burden and mortality and individual and population-level strategies to reduce mortality. The considerable variability in mortality rates within subpopulations of people with HCV will be outlined, such as in people who inject drugs and those with HIV co-infection.

KEYWORDS: Hepatitis C virus, assessment, treatment, care, barriers

The next decade will be a crucial period in the public health response to hepatitis C virus (HCV) infection. The rapid development of direct-acting antiviral (DAA) therapy for chronic HCV infection has brought considerable optimism to the HCV sector,1 with the realistic hope that therapeutic intervention will soon be more effective and offer shorter treatment duration. The initial phase of combination pegylated interferon (PEG-IFN), ribavirin, and one or more DAA agents will be associated with increased toxicity and complexity of therapeutic management,1 but over the course of this decade, strategies including interferon-free regimens with enhanced tolerability, dosing schedules, and simplified monitoring protocols should emerge.

These therapeutic advances are urgently required, as a high HCV incidence 20 to 30 years ago is now reflected in a growing burden of advanced HCV-related liver disease.2-8 Without effective therapeutic intervention, the projected liver disease burden will continue to rise in many countries,9-14 for at least the next one to two decades, and beyond in those settings that have experienced ongoing high-level HCV transmission.

Despite the prospect of greatly improved therapies, the challenges ahead for HCV infection are considerable. HCV treatment uptake is very low in many countries12,15,16 and within marginalized subpopulations in countries with higher treatment uptake.16-20 The explanations for low uptake are multifactorial21 and not the focus of this review, but interferon-related toxicity, lack of HCV treatment infrastructure, suboptimal government subsidization programs and medical insurance coverage, as well as competing patient health

1Viral Hepatitis Clinical Research Program, The Kirby Institute for Infection and Immunity in Society, The University of New South Wales, Sydney, Australia.

Address for correspondence and reprint requests: Professor Gregory J. Dore, The Kirby Institute for Infection and Immunity in Society, University of New South Wales, CFI Building, Corner of Boundary and West Streets, Sydney NSW 2010, Australia (e-mail: gdore@kirby.unsw.edu.au).
and social priorities are likely to remain as contributing factors in the near future.

An improved understanding of morbidity and mortality among people with HCV infection will guide clinical management and therapy decision-making, both at the individual patient and population strategic levels. This review will provide updated information on the natural history of HCV infection, disease-specific causes of mortality among people with HCV infection, estimates and projections of HCV-related disease burden and mortality, the potential impact of HCV treatment on disease burden, and individual and population-level strategies to reduce mortality. The considerable variability in mortality rates within subpopulations of people with HCV will be outlined, and a particular focus given to the issue of competing mortality risk among people who inject drugs and those with human immunodeficiency virus (HIV) co-infection.

NATURAL HISTORY OF CHRONIC HCV INFECTION

An estimated 75% of people who acquire HCV infection progress to development of persistent of chronic HCV infection,22 with associated risk of progressive liver disease, cirrhosis, liver failure, or hepatocellular carcinoma.23 The remaining 25% of people achieve spontaneous HCV clearance22; however, these individuals may be reinfeated in the setting of ongoing HCV exposure. Although many of those with reinfection undergo subsequent spontaneous viral clearance, others develop persistent infection.24–30

As reviewed elsewhere,31 the risk of HCV-related liver disease morbidity and mortality depends on several factors: (1) the duration of HCV infection32–34; (2) the presence of cofactors for development of liver fibrosis (such as male gender35–37 ethnicity38,39 older age at infection37,40–42 heavy alcohol intake,33–45 HIV46–49 or chronic hepatitis B virus (HBV) co-infection,50,51 diabetes,52,53 obesity,54,55 and hepatic steatosis56,57; (3) access to HCV therapy and a favorable treatment response58; and (4) competing mortality risk (such as HIV7,49 and illicit drug-related overdose2,6–8,49). The generally slowly progressive nature of chronic HCV, with limited advanced liver disease in the initial 10 to 15 years of infection (even in those individuals with cofactors for fibrosis development), means that duration of HCV infection and its surrogate, age, are key determinants of mortality risk.31 Thus, a 50-year-old individual with 30 years chronic HCV is likely to have a higher HCV-related mortality risk, even in the absence of liver disease cofactors, than a 30-year-old individual with 5 to 10 years infection and several cofactors. However, the 50-year-old individual with 30 years infection, with heavy alcohol intake, obesity, and regular cannabis smoking (recently shown to be a liver fibrosis cofactor59) will be at particularly high risk.

The risk of HCV-related cirrhosis based on duration of infection has recently been estimated through large systematic reviews of disease progression studies in HCV mono-infected and HIV/HCV co-infected populations (Fig. 1).33,34 The exponential relationship between duration of infection and cirrhosis relates to the generally protracted disease course (few very fast progressors), the cumulative nature of cirrhosis prevalence (even linear rates of progression lead to a nonlinear/upward curve for cirrhosis), and the potential for more rapid fibrosis progression at older age.

Without therapeutic intervention, an estimated 7 to 18% of HCV mono-infected individuals will develop cirrhosis over a 20-year infection period,31,34 and be at considerable risk of HCC (1–6% per annum) or liver failure (2–3% per annum).31 Thus, a significant minority of people with chronic HCV (possibly 10–20%) are likely to have shortened life expectancy through HCV-related mortality. A further large proportion will have HCV-related morbidity with reduced quality of life.60

CAUSES OF MORTALITY AMONG PEOPLE WITH HCV INFECTION

The distribution of causes of death within a population with a chronic disease will depend on several factors: (1) disease-specific natural history and mortality risk, (2) distribution of duration of chronic disease within the population, (3) access to effective therapeutic intervention that alters natural history, and (4) age distribution and competing mortality risk within the population.

The three major disease-specific groupings for mortality among people with HCV infection are drug-related, liver disease-related, and HIV-related. Drug-related mortality includes drug overdose and suicide. Liver disease-related mortality includes decompensated cirrhosis and HCC. The mortality distribution based on these major groupings in population-based HCV noti-
fication—death registry linkage studies in Australia (New South Wales), Sweden, Scotland and Denmark (Lars Omland, personal communication, August 11, 2011) is shown in Fig. 2. In these four countries, the proportion of liver disease-related deaths varied from 19 to 24%, and for drug-related from 18 to 27%. A high proportion of drug-related mortality is consistent with injection drug use (IDU) being the major mode of HCV acquisition in all four settings. The proportion of HIV-related deaths was highest in Scotland (7.9%) where 4% of the HCV-notified population was HIV co-infected, and lowest in Australia (0.4%) where only 0.5% was HIV co-infected. Settings in which the HIV co-infection rate is even higher than Scotland, such as in developed countries in North America and Europe, would be expected to have larger proportions of deaths related to HIV disease.

Temporal trends in mortality rates and distribution among people with HCV infection are clearly important to monitor. From 1992 to 2006 in New South Wales, Australia, there has been a steady increase in the number of people with HCV dying from liver-related causes (Scott Walter, personal communication, August 11, 2011) (Fig. 3). In contrast, the number of deaths from drug-related causes increased rapidly during the 1990s, but has declined since 1999 due to the well-documented heroin “drought” starting in late 1999 and its likely subsequent reductions in IDU. The number of liver disease-related deaths reflects the expanding pool of chronic HCV including larger numbers with prolonged duration of infection (aging cohort effect). From 1997 to 2006 the age-adjusted liver disease mortality rate was stable (around 15 deaths per 10,000 person years), indicating no impact of improved HCV therapy. The lack of an effect of HCV treatment on individual risk of liver-disease mortality probably relates to the generally low-treatment uptake rate, suboptimal efficacy (particularly among those with advanced liver disease), and the relatively short period of follow-up since improvements.

Consistent with increasing numbers of people with HCV dying from liver-related causes, the proportion of all liver disease deaths with underlying HCV is increasing in many settings, as demonstrated in a population-based study in Scotland. The burden of HCV-related advanced liver disease is also seen in increasing numbers of HCV-related liver transplants in many countries.

Mortality among Injection Drug Users with HCV infection

The prevalence of HCV among regular IDUs and people receiving opioid substitution therapy (OST) is 60 to 80%; thus, mortality studies in these populations are likely to reflect mortality among IDUs with HCV infection. Overall, mortality rates in these two populations are 1 to 2 per 100 person years, although there is evidence that OST reduces drug-related mortality. A study among the OST population in Australia demonstrated a considerably higher drug-related mortality rate compared with liver-disease mortality, with the ratio varying from threefold when receiving OST to 18-fold when not receiving OST. However, this study covered a period during the 1990s with very high rates of drug-related mortality. A more recent mortality linkage study in New South Wales that included people on OST in 1980 to 1984 has demonstrated increasing rates of liver disease mortality, which in recent years is the leading cause of death overtaking drug-related mortality. This study is of great importance as it demonstrates the impact of liver disease on mortality within an aging cohort, particularly when rates of IDU decline.

In Canada, the Vancouver community-based CHASE cohort (81% and 42% have used illicit and injection drugs in the past 6 months; HCV prevalence is 64%) has also examined all-cause and liver-related mortality through data linkage to a death registry. Between 2003 and 2007, the rate of mortality was 1.9 per 100
person-years, with causes of death being 7% liver-related, 20% drug-related, 21% HIV-related, and 52% other cause-related. All-cause mortality was associated with age > 50 years and HIV infection. Further, those > 50 years of age were at significant risk of liver-related mortality. Given that many communities of IDUs were infected with HCV in the 1970s and 1980s, there will inevitably be greater incidence of liver disease over the next decade.

The potential future burden of advanced liver disease within aging cohorts is also reflected in an autopsy study among individuals dying from opioid toxicity in New South Wales, Australia.67 Among 841 deaths over a 5-year period (1998–2002), the HCV prevalence was 71% and cirrhosis was present in 7%.67 However, in those aged > 44 years at death (n = 75), cirrhosis prevalence was 25%.

Mortality in Other Populations with HCV Infection
Injection drug use has been the major mode of HCV acquisition in North America, Europe, and Australia. However, in other settings, HCV transmission has largely been through non-IDU modes and the contribution of drug-related mortality is therefore considerably reduced. Thus, the impact of HCV-related disease on mortality rates and distribution is more evident.

In one study from the United Kingdom, 924 individuals who had acquired HCV infection via blood transfusion were traced during a look-back program.68 By the end of 2004, 28% had died (255 of 924), with 26% dying of liver-related causes. The risk of liver-related mortality in those with HCV infection was three times higher than the control group of anti-HCV negative transfusion recipients. In Taiwan, 23,785 persons (aged 30 to 65 years, HCV prevalence 4.5%) were recruited from seven townships between 1991 and 1992 and followed through 2004.69,70 Among participants with HCV mono-infection (n = 1,040), 171 died by 2004; 28% of deaths were liver-related. After adjusting for gender, age, cigarette smoking, and alcohol consumption, those with HCV mono-infection were two times more likely to die of any cause and five times more likely to die of chronic liver disease and cirrhosis compared with those without HCV. These data suggest that HCV still leads to excess mortality when drug-related and HIV effects are removed.

Mortality in People with HIV/HCV Co-Infection
As reviewed elsewhere,71 co-infection with HIV decreases spontaneous clearance of HCV infection,72 increases HCV RNA levels,73 increases HCV-related liver disease progression,46,74 and reduces response to IFN-based therapy.75,76 Since the introduction of triple-combination antiretroviral therapy in the mid-1990s, overall mortality rates among HIV-infected populations have declined dramatically.77 Further, the distribution of causes of death have altered considerably, with a declining proportion of acquired immunodeficiency syndrome- (AIDS-) related mortality and increasing proportions of cardiovascular and liver disease mortality.78,79 The contribution of liver disease to mortality is particularly high in settings with a high HIV/HCV co-infection prevalence73; however, even in Australia where only 10 to 15% of people with HIV are HCV co-infected, liver disease contributes to 11% of deaths (Kathy Petoumenos, personal communication, August 12, 2011).

Within the HIV/HCV co-infected population, factors that influence rates and distribution of mortality are access to antiretroviral therapy, access to and effectiveness of HCV therapy, drug use, and age distribution.71 In Australia, within the HIV/HCV co-infected population there is universal access to antiretroviral therapy and high levels of uptake, relatively limited regular ICU (the vast majority are men who have sex with men), and an aging population. Among HIV/HCV co-infected patients enrolled in the Australian HIV Observational Database (AHOD; n = 3,531), liver disease has been the underlying cause in 26% of deaths (14 of 55 deaths) as compared with only 9% of deaths (16 of 181) in those with HIV alone (Kathy Petoumenos, personal communication, August 12, 2011).

Further, although the lifespan of those with HIV infection has been improved through the availability of contemporary antiretroviral therapy, the lives of those with HCV/HIV co-infection remain much shorter.71 In Denmark, one study compared the mortality rates of 3,990 HIV-infected persons and the general population.80 The study demonstrated that although mortality has dropped significantly in HIV-infected persons (from a high of 124 per 1000 person years in the era preceding HIV antiviral therapy to 25 per 1000 person years in 2000–2005), the impact was less pronounced among those co-infected with HCV (57 per 1000 person-years in those with HCV/HIV vs 19 per 1000 person-years among those with HIV alone). In a large study of 23,441 HIV-infected persons (76,893 person-years of follow-up), the frequency of and risk factors associated with liver-related deaths were assessed (66% with HCV co-infection, 17% active HBV co-infection).78 Among 1246 deaths (5.3%; 1.6 per 100 person-years), liver-related death was the most frequent cause of non-AIDS related death (14.5% were from liver-related causes). Predictors of liver-related deaths were latest CD4 cell count, older age, IDU, HCV infection, and active HBV infection. Given the underreporting of liver-related disease, the actual impact is probably even greater.71
THE POTENTIAL IMPACT OF IMPROVING HCV THERAPY ON MORTALITY RATES

The burden of HCV-related advanced liver disease is projected to increase further in many countries. A major public health issue is the potential impact of improving HCV therapy on these projected increases in mortality. In HIV, the availability of effective combination antiretroviral therapy from the mid-1990s dramatically reduced the overall mortality rate and altered the distribution of causes of death (increasing proportion of non-AIDS related deaths). Despite treatment success of 70 to 80% and shorter duration therapy (generally 24 weeks), the lower overall disease-specific HCV mortality risk compared with HIV and more protracted disease progression (life expectancy for chronic HCV infection is on average reduced by several years rather than decades for HIV) mean that a more-effective and more broadly implemented therapeutic intervention will be unable to have the dramatic impact that was seen for antiretroviral therapy. However, there is considerable potential for improved HCV therapeutic intervention to alter expected HCV-related mortality, particularly when the temporal “ageing cohort” effect is most pronounced.

The recent introduction of DAA therapy in combination with PEG-IFN and ribavirin will enhance treatment response rates for those with chronic HCV genotype 1 infection and shorten duration of therapy for many patients. However, low HCV treatment (PEG-IFN/ribavirin) uptake rates for those with chronic HCV genotype 2/3,12,15–20 despite treatment success of 70 to 80% and shorter duration therapy (generally 24 weeks), suggest that initial DAA-based response rate improvements will have a modest impact at the population level. Recent evidence suggests that IFN-free combination DAA therapy with high rates of treatment response is feasible.81 Improvements in DAA therapy tolerability and dosing schedules are highly likely given agents in phase II/III development.81 Large population-level impacts on HCV-related liver disease mortality will likely require IFN-free combination therapy that is tolerable, has a favorable dosing schedule, and is effective over a relatively short duration. Such HCV therapeutic advances are within reach over the next decade.

HOW CAN WE CURRENTLY PREVENT PEOPLE WITH HCV INFECTION FROM DYING?

The availability of PEG-IFN/ribavirin–free regimens for the treatment of HCV infection are still 5 to 10 years away and other strategies will be required if we are to stem the projected rise in liver-disease burden. Strategies that increase the proportion of individuals diagnosed, assessed, and treated for HCV infection with currently available treatment regimens are required.

Increasing the number diagnosed with HCV infection will be important as we move forward. In the United States, the true number of people infected with HCV is likely underestimated (5.2 million as compared with previous estimates of 3.3 million from household surveys), given that homeless people, prisoners, IDUs, and other marginalized populations at high-risk of HCV are often not included in national household surveys. Strategies to enhance diagnosis of HCV may include the promotion of national HCV testing guidelines, and enhanced education and training of general practitioners about HCV testing and diagnostic criteria to enhance diagnosis and referral. Further strategies include the provision of mentoring diagnosis programs among general practitioners with higher case loads of HCV-infected patients, an improved awareness of programs offering comprehensive multidisciplinary HCV care (particularly for IDUs), and improved pathways for referral. Incorporation of HCV assessment and treatment services into drug and alcohol treatment settings is also required.

Enhancing the proportion assessed for HCV is crucial. Non-invasive tests of fibrosis (e.g., FibroScan and FibroTest) offer considerable opportunities for enhanced screening and assessment of liver disease. In a study at one hospital in France, a cohort of 1457 consecutive patients with chronic HCV were assessed for liver fibrosis by liver biopsy, FibroScan, FibroTest, aspartate aminotransferase to platelet ratio index (APRI), and FIB-4 score to evaluate all-cause and liver-related mortality during a 5-year follow-up period.85 Survival was significantly decreased among patients diagnosed with severe fibrosis (regardless of the noninvasive method employed) and all noninvasive methods were able to predict shorter survival times, although FibroScan and FibroTest had higher predictive values. These tools will help physicians determine prognosis at earlier stages and therefore allow enhanced targeting of therapy to those with significant liver disease.

Strategies are needed to enhance HCV assessment and treatment in the community to reduce mortality among people with HCV. Barriers to expanding HCV treatment in the community are multifactorial and include issues of access to therapy and barriers at the level of the patient, practitioner, and system. HCV-infected patients often have complex social, medical, and psychiatric comorbidities, complicating decisions around care. Currently, there is limited infrastructure for the provision of HCV assessment and treatment delivery beyond well-established, hospital-based liver clinics. However, successful strategies to improve engagement with HCV services and enhance HCV assessment have been explored. One model to enhance access to HCV care for underserved populations focused on the integration of community-based health centers in New Mexico using state-of-the-art telehealth technology to provide training and support for primary
care providers to deliver best-practice HCV care.\textsuperscript{87} This model was effective, with similar responses to HCV treatment observed among community-based clinics as compared with a university-based hospital.\textsuperscript{87} This approach represents a needed change from the conventional approaches in which specialized care and expertise are concentrated in academic medical centers in urban areas. Lastly, given that 70 to 80\% of current HCV infections occur among IDUs,\textsuperscript{88} it is clear that strategies to reduce mortality among those living with HCV will require specific strategies for this marginalized group. There is now overwhelming evidence that the treatment of HCV infection in this population is safe and effective for reducing mortality among those living with HCV will require specific strategies for this marginalized group. There is now overwhelming evidence that the treatment of HCV infection in this population is safe and effective across multiple models of care.\textsuperscript{89} As such, older IDUs in particular will be an important group to follow clinically (perhaps with noninvasive liver fibrosis screening) and perhaps offer intensified HCV assessment and treatment in an effort to reduce liver-related mortality.

CONCLUSION

Our understanding of morbidity and mortality among people with HCV infection has greatly improved over the past several decades. In large population-based studies, liver-related and drug-related causes of death account for approximately one-half of all deaths (one-quarter each) among people with HCV infection. Liver disease burden continues to rise in many countries,\textsuperscript{9–14} particularly given the low HCV treatment uptake in many countries\textsuperscript{12,15,16} and sub-populations.\textsuperscript{16–20} Although novel HCV treatments (particularly PEG-IFN/ribavirin-free regimens) offer great hope for reducing the future mortality associated with HCV, combinations with improved tolerability and shorter duration are still 5 to 10 years away. Current efforts will need to focus on enhancing the diagnosis, assessment, and treatment of HCV-infected patients at greatest risk of liver disease progression to reduce mortality among those living with HCV infection.

ABBREVIATIONS

AIDS acquired immunodeficiency syndrome
DAA direct-acting antiviral
HBV hepatitis B virus
HCV hepatitis C virus
HIV human immunodeficiency virus
IDU injection drug use
PEG-IFN pegylated interferon

REFERENCES

13. NCHECR. Epidemiological and economic impact of potential increased hepatitis C treatment uptake in Australia. Sydney, Australia: National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales; 2010
18. Grebely J, Genoway K, Khara M, et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary...
47. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis 2001;183(7):1112–1115


