Federal Government Standing Committee on Health
Inquiry into Hepatitis C in Australia

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This submission relates to the following terms of reference:

1. Prevalence rates of Hepatitis C in Australia
2. Hepatitis C early testing and treatment options
3. The costs associated with treating the short term and long term impacts of Hepatitis C in the community

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Hepatitis C prevalence and disease burden

The number of new HCV diagnoses declined from 11 480 in 2009 to 10 698 in 2013. Declines have been observed in all age groups. In the past ten years, the rate declined in most age groups but most prominently in the 25 – 29 year (by 50%), and 20 – 24 year (by 43%) age groups.

In contrast to low HIV prevalence (1-2%) among people who inject drugs (PWID), HCV prevalence among PWID attending needle and syringe programs remained high during 2004 – 2013. However, HCV prevalence decreased among both males and females from around 62% in 2008 to around 53% in 2009 and has remained stable since 2009.

The proportion of people attending needle and syringe programs who reported having initiated injection drug use in the previous five years remained stable at 9% – 13% between 2009 – 2013; HCV prevalence among this group (new initiates) declined from 20% in 2009 to 14% in 2013. The low proportion of new initiates and the low proportion of survey respondents aged younger than 20 years (around 2% in 2013) suggests a decrease in the prevalence of injecting drug use among young people in Australia.

The estimated number of new HCV infections has declined from 10 300 in 2003 to 5 400 in 2013. This decline in HCV incidence (total infections per year in Australia) would appear to relate to both a reduction in the number of people injecting drugs, particularly young people initiating use, and improved harm reduction including enhanced access to opioid substitution treatment (methadone, buprenorphine). Improved harm reduction has led to a decline in HCV incidence among community-based PWID (risk of infection per individual). Similar declines have not been documented among incarcerated PWID.

In 2013, an estimated 230 000 people were living with chronic HCV, including around 80 000 with at least moderate fibrosis, clear evidence of progressive liver disease, and around 15,000 with cirrhosis and its complications (liver failure, primary liver cancer - hepatocellular carcinoma/HCC). Although HCV-related liver disease is the most common reason for liver transplantation in Australia, and the number of HCV-related liver transplants is increasing, the lack of sufficient donor livers means that only a small minority of those people with liver failure or HCC are eligible and receive a transplant (91 in 2013). An estimated 630 people died in 2013 from HCV-related liver disease complications.

Table 1: Key HCV epidemiological parameters in Australia: 2013

New HCV infections (estimated)	5,400
New HCV diagnoses	10,698
Percent of HCV infections diagnosed (estimated)	85%
HCV prevalence among PWID (ANSPS attendees)	54%
Chronic HCV prevalence (estimated)	230,000
F0/1 (no/mild fibrosis)	155,000
F2 (moderate fibrosis)	36,000
F3 (severe fibrosis)	28,000
F4 (cirrhosis)	11,400
Decompensated cirrhosis/liver failure (estimated)	2,600
Hepatocellular carcinoma (HCC) cases (estimated)	450
Liver-related deaths (estimated)	630
HCV-related liver transplants	91
Number of HCV treatment initiations	3,200

The burden of HCV-related advanced liver disease is rising rapidly

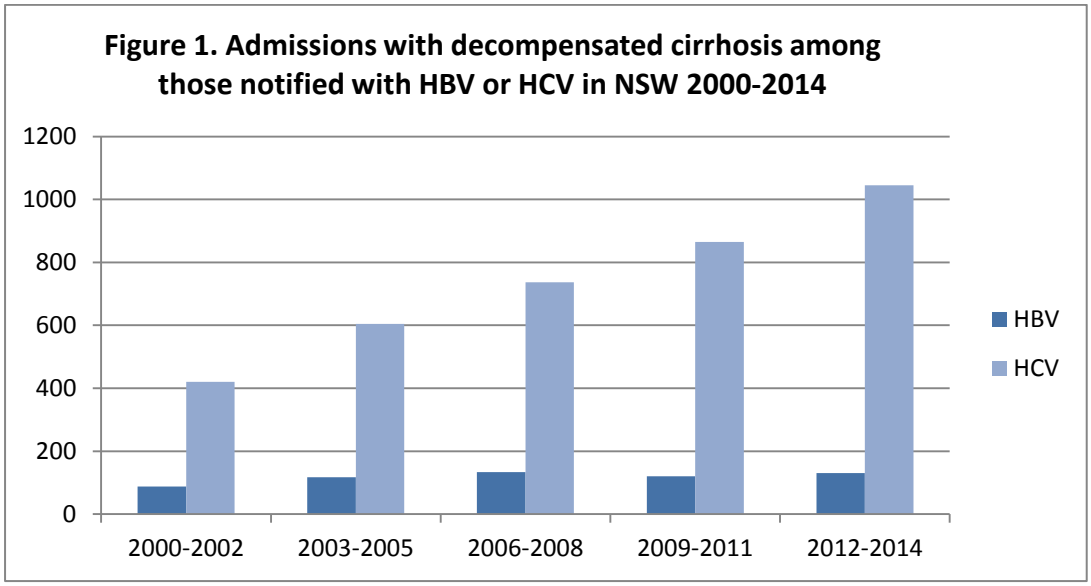
The HCV-related liver disease burden in Australia is rising rapidly. The estimated numbers of people living with cirrhosis, and developing complications of decompensated cirrhosis (liver failure) and primary liver cancer (hepatocellular carcinoma, HCC) have more than doubled over the past decade. This relates to three key aspects of the HCV epidemic in Australia:

1. Large and growing chronic HCV population, despite recent declines in HCV incidence;
2. Ageing chronic HCV population, as those infected in 1970-1980s have now been infected for 20-30 years (median time for progression to cirrhosis and complications);
3. Low HCV treatment uptake (1-2% per annum over last decade) and sub-optimal treatment efficacy, particularly in advanced liver disease.

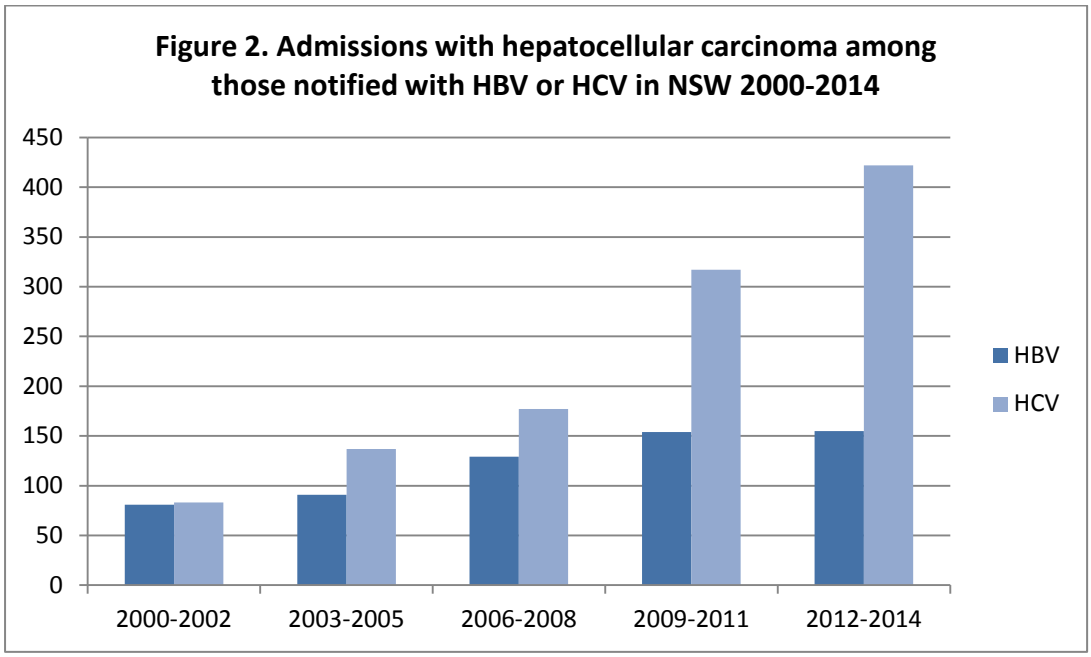
The most comprehensive information on HCV-related liver disease burden comes from NSW where the Kirby Institute has conducted three major rounds of data linkage between the NSW notifiable diseases database, hospitalisation database, cancer registry, and national death index. The most recent round has completed preliminary analyses based on around 100,000 HCV notifications and demonstrates continued rising burden of advanced liver disease. For example, the number of people with hospitalisation for a first episode of HCV-related decompensated cirrhosis (liver failure) has increased from around 400 in 2000-2002 to more than 1,000 in 2012-2014 (Figure 1). These figures do not include hospitalisations for subsequent episodes of decompensated cirrhosis, often several within an individual patient.

Of note, the number of people hospitalised for a first episode of HBV-related decompensated cirrhosis has stabilised over the same period (Figure 1), almost certainly due to the introduction of progressively improved HBV antiviral therapy during this period. Key aspects of the most commonly used HBV antiviral therapies (tenofovir, entecavir) are oral formulation (one tablet per day), limited side effects, high viral suppressive efficacy, and capacity for use in people with liver failure. In contrast, current interferon-based HCV therapies have sub-optimal efficacy in cirrhosis and are unable to be used in liver failure. One of the most exciting features of the new interferon-

free direct acting antiviral (DAA) therapy regimens for chronic HCV are their high efficacy in cirrhosis and capacity for use in decompensated cirrhosis.



The escalation in initial hospitalisation for HCV-related hepatocellular carcinoma (HCC) has been even more dramatic, increasing from less than 100 cases in 2000-2002 to more than 400 cases in 2012-2014. HCC is the only cancer in Australia with such a trajectory, largely driven by chronic HCV. Given that HCC-related survival is so poor (median survival 12-15 months), the rise in incidence of HCC is paralleled by similar rises in deaths from HCV-related HCC.

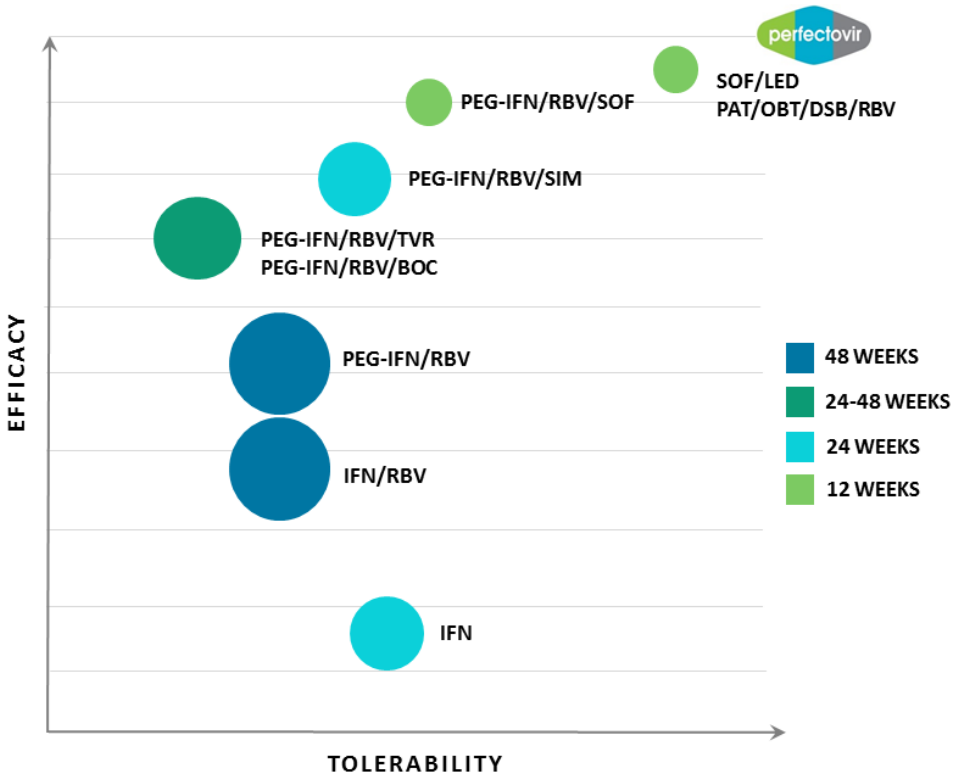


Hepatitis C treatment options

Chronic HCV treatment has been interferon-based for the last two decades, with the addition of ribavirin (RBV), Pegylated interferon (PEG-IFN), and initial protease inhibitor direct acting antiviral (DAA) therapies (telaprevir, boceprevir) providing stepwise improvements in the rate of sustained virological response (SVR, equivalent to cure of infection)(Figure 3). Despite these improvements in interferon-containing regimens, treatment uptake has remained low in Australia with 1-2% treated per year. Multiple factors have contributed to low HCV treatment rates, including sub-optimal efficacy, medical co-morbidities and therapeutic toxicity, prolonged duration of therapy (24-48 weeks), lack of awareness of the curative potential of treatment, lack of treatment infrastructure, social marginalization of many people with chronic HCV, and low rates of HCV disease assessment. Lower HCV treatment response rates in advanced liver disease have also limited the impact on disease burden.

Fortunately, recent years have seen a revolution in HCV therapeutic development, with the advent of DAA therapy and the move towards interferon-free regimens. Within a few years, simple (single daily dosing oral regimens), highly tolerable, short-duration (6-12 weeks) therapy with extremely high efficacy (cure rates above 90%) should be the norm as we head towards “perfectovir”. The broad implementation of such therapeutic regimens has the potential to produce one of the major turnarounds in disease burden seen in public health and clinical medicine.

Figure 3. HCV therapuetic development in relation to efficacy, tolerability and duration



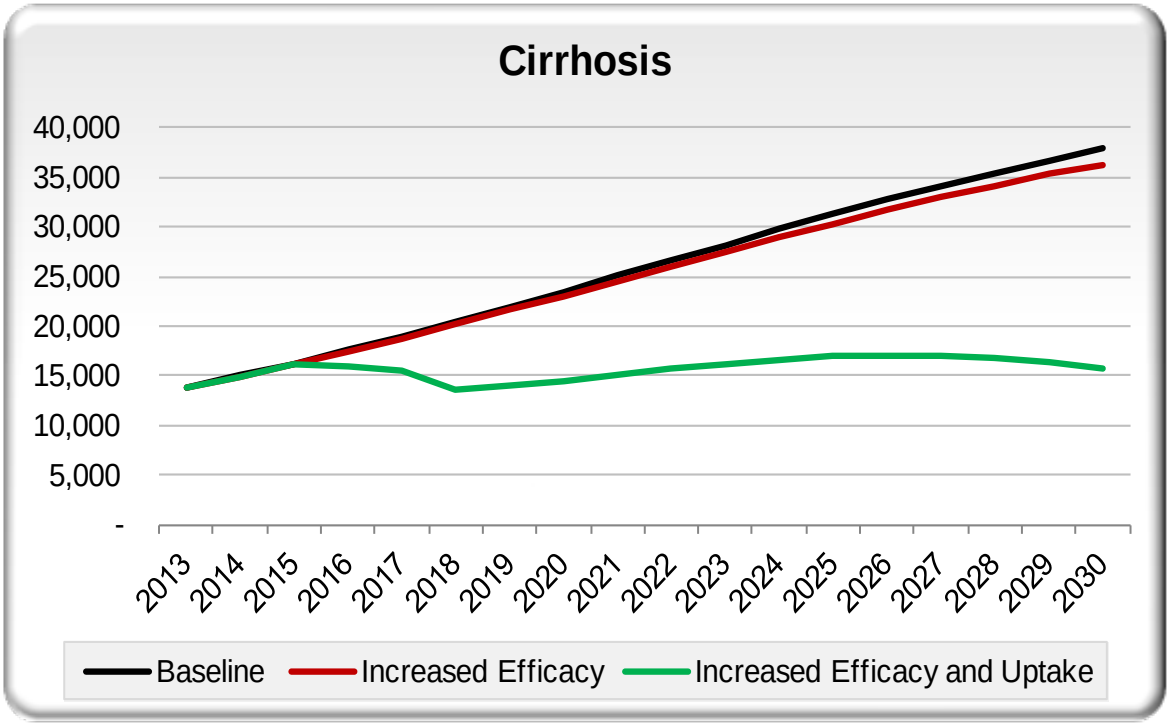
IFN=interferon; RBV=ribavirin; PEG-IFN=pegylated interferon, TVR=telaprevir, BOC=bocpeprevir, SIM=simeprevir, SOF=sofosbuvir, LED=ledipasvir; PAT=parateprevir, OBT=ombitasvir, DSB=dasabavir

To optimise the potential benefit of new interferon-free DAA regimens, once subsidised, several key barriers to broadened HCV treatment access should be addressed:

1. **Removal of restriction on S100 HCV treatment prescription to specialist physicians**
   Kirby Institute undertook a quantitative evaluation of the NSW Primary Care Prescriber Pilot Project which clearly demonstrated that equivalent HCV treatment outcomes can be achieved by appropriately trained general practitioners. The use of interferon-free DAA regimens would be even more suitable for primary care delivery, given reduced toxicity and ease of delivery.
2. **HCV treatment education for general practitioners and addiction medicine specialists**
   Kirby Institute led the ETHOS project which demonstrated relatively high HCV treatment uptake (25% of those HCV assessed by nurse or clinician) and equivalent HCV treatment outcomes to tertiary clinic settings for people with HCV in opiate pharmacotherapy (methadone/buprenorphine) and community-based clinics. Investment in HCV treatment education for general practitioners (particularly those prescribing methadone /buprenorphine) and addiction medicine specialists, together with investment in HCV treatment infrastructure in opiate pharmacotherapy settings is required.
3. **Community-based education**
   Although knowledge of new HCV therapies would appear to be improving among people living with HCV, a community-based education program could highlight the transformative nature of new therapies once subsidised and promote HCV assessment. Liver disease assessment is of particular importance for those aged over 40 years, who clearly have a higher risk of progressive or advanced liver disease.
4. **Peer support worker involvement**
   HCV and injecting drug use are highly stigmatised, providing some explanation for the low levels of HCV disease assessment among PWID (particularly those who are currently injecting). The ETHOS project also demonstrated the value of peer support to PWID to enhance knowledge of HCV, and play an important conduit (and advocate) between patient and health care professionals.

The current level of HCV treatment (around 3,200 people initiated per year) in Australia will have a limited impact on the rising burden of advanced liver disease. Modelling undertaken by the US-based Center for Disease Analysis (CDA) in collaboration Australian hepatologists and the Kirby Institute clearly demonstrates the need for an increase in both HCV treatment efficacy and uptake to prevent further increases in cirrhosis and its complications. Introduction of interferon-free DAA regimens, with cure around 90%, would have minimal impact on disease burden if treatment rates remain unchanged (increased efficacy scenario). In contrast, introduction of interferon-free DAA regimens from 2015, with initial targeting (2015-2017) to those with more advanced liver disease (severe fibrosis/F3, cirrhosis/F4) and progressive increases in uptake to 14,200 people treated per year by 2018 (four to five-fold increase) would lead to no further increases in number of people with cirrhosis (Sievert W et al. JGH 2014)(Figure 4). Similar trends are evident for liver failure, primary liver cancer (HCC), and liver-related deaths. For example, under the current treatment scenario the number of people with HCV dying from liver failure and HCC will double by 2024. Further modelling indicates that even a one year delay in introduction of interferon-free DAA regimens could lead to an additional 900 deaths, with 1,800-2,000 additional deaths with a two year delay.

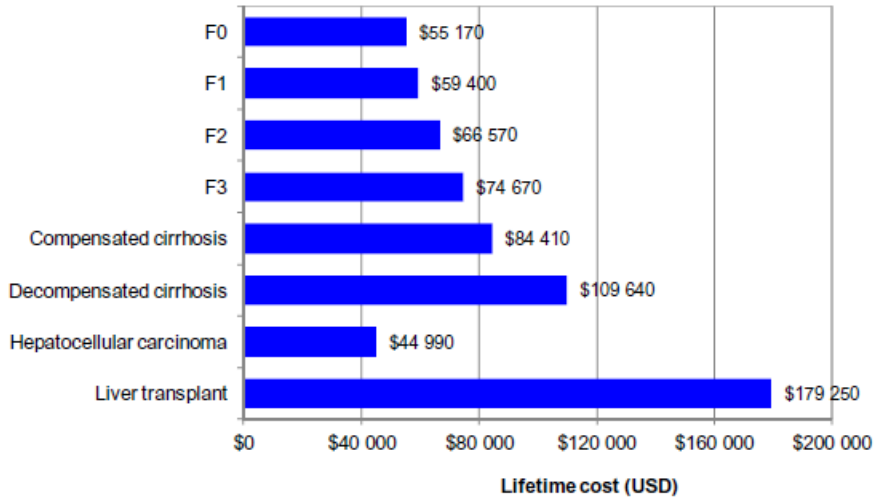
Figure 4. Estimated number of people living with HCV-related cirrhosis in Australia



Hepatitis C and healthcare costs

The burden of chronic HCV relates to reductions in health related quality of life (HRQOL), even at early stages of liver disease, and the impact of progressive liver disease that leads to cirrhosis in 20-30% of people within 20-40 years infection. People with cirrhosis clearly have impaired HRQOL, which is further impaired through development of liver failure or hepatocellular carcinoma (HCC). The lifetime healthcare cost relates to the liver disease stage, with considerably higher costs for those people who progress to advanced liver disease, as demonstrated in research work undertaken by CDA in collaboration with Australian hepatologists and Kirby Institute (Figure 5, Sievert W, et al. JGH 2014). The relatively low lifetime healthcare cost associated with HCC relates to the extremely short survival and lack of curative treatment options for most people.

Figure 5. Estimated lifetime costs by liver disease stage



Are the new interferon-free DAA regimens cost effective?

A crucial requirement for the HCV response is development of HCV treatment regimens that are affordable for healthcare systems, and provide a return on investment for the pharmaceutical industry, an essential driver of ongoing therapeutic development. US pricing of sofosbuvir ($US 84,000 for 12 weeks) and simeprevir ($US 66,000 for 12 weeks) following FDA licensure in late 2013 provided a high threshold for HCV treatment in high income countries, particularly given the subsequent “off-label” use of sofosbuvir plus simeprevir. Recent HCV drug pricing has generated significant controversy, leading to widespread media coverage and restrictions on access to new therapies by third party and governmental payers. Although these highly effective DAA regimens are cost-effective by standard public health intervention criteria (less than $50,000 USD per quality adjusted life-year saved is generally used), the greatly enhanced potential demand of interferon-free DAA regimens has raised concerns regarding their impact on healthcare budgets.

Antiviral therapy for HBV and HIV generally requires several years to decades of ongoing therapeutic investment to optimise health benefits. However, the health benefits that can be achieved through short duration curative HCV therapy and pricing on a per unit basis leads to extremely high per pill and “up-front” costs. HCV therapy cost-effectiveness is largely driven by prevention of downstream costs, in particular complications of advanced liver disease (decompensated cirrhosis, HCC), but these costs are incurred over decades rather than years.

Under current drug pricing models in high income countries, treating all people with chronic HCV would have a major impact on healthcare budgets. Thus, alternative drug pricing strategies are being considered. The simplest and most commonly adopted policy is restriction to those with more advanced liver disease. Although disease stage-based restrictions may optimise benefits (cost-effectiveness) of therapy, potential downsides include losing patients to follow-up, reduced efficacy in advanced fibrosis (albeit largely overcome with interferon-free DAA regimens), lack of

prevention of extra-hepatic HCV manifestations, and lack of potential quality of life improvement among patients with early liver disease.

Broadened access to highly curative interferon-free DAA regimens in Australia, a prerequisite for preventing the escalating burden of advanced liver disease complications and mortality (as described above), will require two fundamental commitments:

1. **Pharmaceutical industry discounts on United States-listed drug pricing**
   Even in the US, the presence of two competitive regimens for chronic HCV genotype 1 (from Gilead and Abbvie) has led to discounts of 40-50% for large payer entities. These discounts have reduced the price per course (generally 12 weeks duration) to around $US 50,000.
2. **Greatly enhanced investment in HCV therapeutics by the Australian Government**
   In order to treat around 14,000 people per year (required to prevent further rises in cirrhosis and its complications), even at $AUS 45,000 ($US 35,000 or around 60% discount) would require an investment of $630 million per year, a seven-fold increase on current expenditure ($85-90 million per year).

Recent modelling has been undertaken by a CDA – Kirby Institute collaboration to examine the direct healthcare costs of chronic HCV and related treatment costs under various scenarios. The average cost of current treatment was estimated at $30,000 per patient after taking into consideration the different treatment options (PEG-IFN/RBV, PEG-IFN/RBV/simeprevir) and the genotype distribution in Australia (55% G1/4 and 45% G2/3).

Scenarios: A number of different treatment scenarios were assessed for this analysis. The base scenario was based on current treatment guidelines. In addition, three different price points for IFN-free DAA therapy were assessed – average price across all genotypes of $38,000, $45,000 and $55,000 per course.

Treatment scenarios: Base scenario was consistent with current estimates of the number of people treated with IFN-containing regimens in Australia and current S100 criteria (i.e. no liver disease stage restrictions). In the ***Increase SVR only*** scenario the same treatment uptake and liver disease stage distribution was used, but with increased treatment efficacy from 2015-2016 related to introduction of IFN-free DAA therapies. In the ***Increase SVR & Tx (>=F3, 2015-2017)*** scenario both treatment uptake and efficacy were increased from 2015, with an initial period (2015-2017) of liver disease stage restriction (F3-4) prior to expansion to all stages. In the ***Increase SVR & Tx (>=F3 only)*** scenario the same parameters were employed, but the initial targeting to F3-4 was continued throughout the study period. Finally in the ***Hybrid*** scenario the treatment uptake and efficacy and liver disease state restrictions were kept the same as Increase SVR & Tx (>=F3, 2015-2017) scenario except that liver disease stage restriction was gradually removed with those >=F2 getting access to the new therapies in 2018 and patients >=F1 getting access starting in 2022.

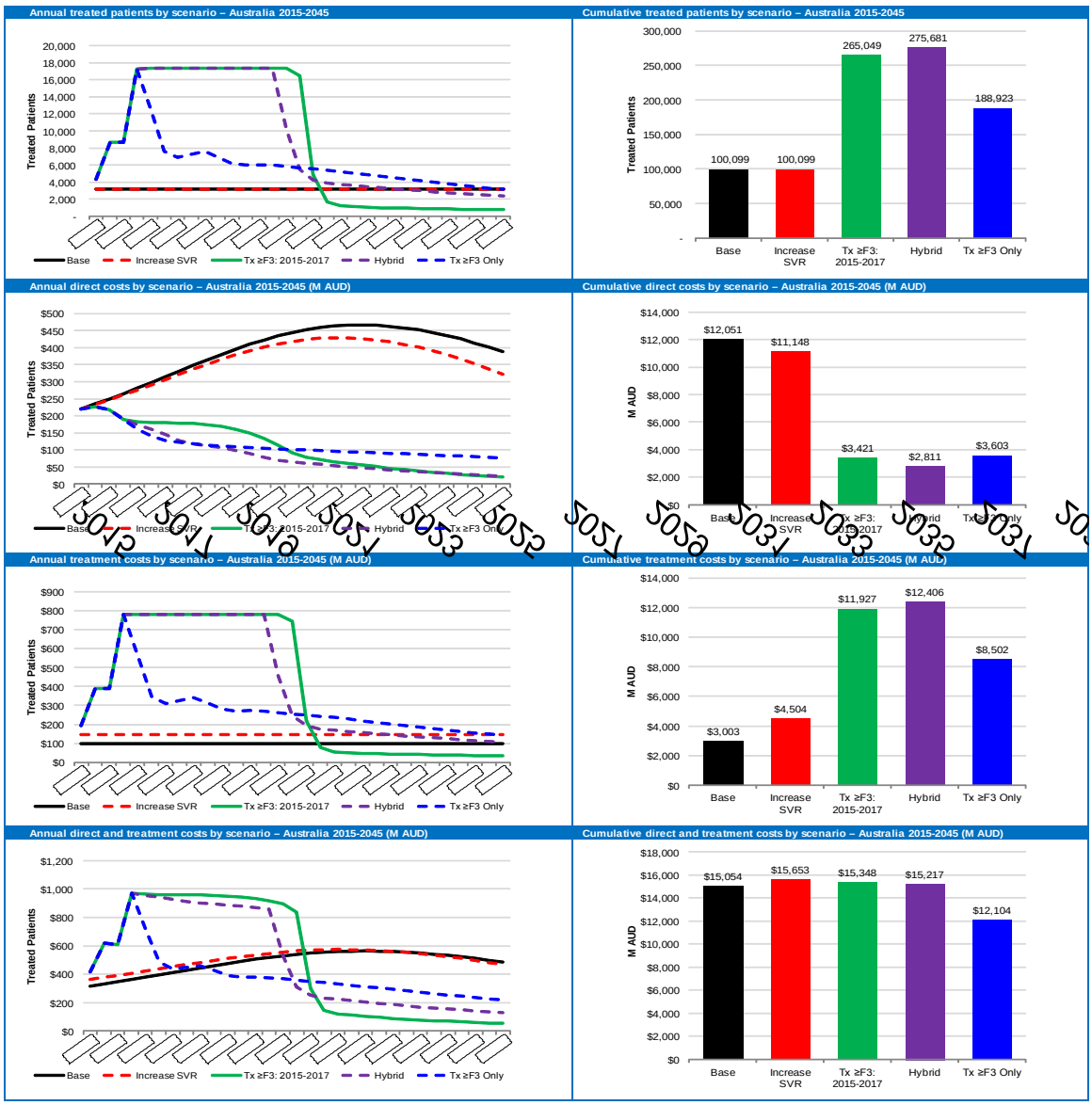
Key findings:

1. Over the next twenty years, the annual direct healthcare costs associated with HCV infection will increase by more than two fold from $220 million per year in 2015 to $470 million per year in 2035. This is the result of the aging of the HCV infected population and progression of patients to end stage liver disease (ESLD) that is more costly to treat and may require liver transplantation.

2. At an average price of $38,000 per course (for IFN-free DAA therapies), every scenario considered was shown to be cost effective/saving over a thirty year period. The high upfront cost of the new therapies is offset by reduction in future healthcare cost as cured patients are much less likely to progress to ESLD.
3. At an average price of $45,000 per course (for IFN-free DAA therapies), the total direct healthcare impact of all scenarios is roughly equivalent to the base scenario with the exception of the scenario where only patients who are ≥F3 are considered for treatment. The ≥F3 scenario is more cost effective than the base scenario over a 30 year time horizon.
4. At an average price of $55,000 per course (for IFN-free DAA therapies), only the strategy that focuses on treatment of HCV infections which are ≥F3 is more cost effective than the current treatment guidelines (base scenarios). All other scenarios will be more expensive.

It should be noted that this study only looked at direct healthcare costs without considering loss of productivity due to aliment or early death nor a quality of life measure.

Figure 6. Direct and treatment health care costs for interferon-free DAA therapy ($45,000)



Conclusion

The advent of highly curative, well tolerated, and simple all oral HCV regimens is one of the most exciting development in clinical medicine in recent decades. It recalls the amazing strides that HIV treatment made from the mid-1990s. Australia has been an international leader in the response to the HIV epidemic, and has a similar opportunity to show leadership in the response to HCV, an infection and chronic disease that impacts the lives of more than 200,000 Australians, a majority of whom remain economically and socially marginalised.

The rising burden of HCV-related liver disease can be prevented, if action is taken quickly, particularly in relation to life-saving new HCV therapies. Economic realities will always dictate the need for public health priorities, however, the ability to cure almost all patients treated with interferon-free DAA regimens will provide enormous empowerment for people living with HCV, health care professionals working with affected communities, and the community at large.