Turning the tide on hepatitis C-related liver transplantation: the return on investment in hepatitis C treatment in Australia and New Zealand

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Abstract

Background: Introduction of universal access to direct-acting antiviral therapy (DAAs) for hepatitis C (HCV) in Australia and New Zealand on March 31st 2016 has had a major impact on the number of people with chronic HCV infection, but the impact on liver transplantation rates is unknown.

Methods: We conducted a retrospective registry study including all adult liver transplants from the Australian and New Zealand Liver and Intestinal Liver Transplant Registry dataset (ANZLITR). Interrupted time series analysis determined the impact of DAAs in 2016 on the number of HCV liver transplants per year. Cox regression analysis was used to determine the impact of DAAs on post liver transplant survival.

Results: Between 1st January 1990 and 31st December 2019, 5318 adult liver transplants were performed, 29% (1531) were for hepatitis C infection. Prior to introduction of DAAs, there was a mean increase of 3.5 adult liver transplants performed for HCV per annum, but between 2016 to 2019 there was a mean decrease of 7.9 adult liver transplants per annum ($p<0.0001$). Similarly, the proportion of liver transplants performed for HCV increased from 9% (1990) to 33% in 2016, then fell to 23% in 2019 ($p<0.001$). The number and proportion of patients with hepatitis C waitlisted for liver transplantation also fell from 2016 ($p<0.001$) comparative to other indications. Introduction of DAAs was associated with a 31% reduction in death after liver transplantation, adjusted for age at transplant and hepatocellular carcinoma (HR 0.69, 95% CI 0.48-0.99, $p=0.047$).

Conclusion: The number of adult liver transplants performed for HCV-related liver cirrhosis and HCC has reduced since introduction of universal access to DAAs in 2016 in Australia and New Zealand.

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Introduction

In Australia and New Zealand, chronic hepatitis C infection (HCV) is a leading cause of death from end stage liver failure and hepatocellular carcinoma (HCC) (1, 2) and has been the most common indication for adult liver transplantation over the last three decades, accounting for 29% of all liver transplants performed (3-5). Historically, HCV was very difficult to treat. Interferon-based therapy was arduous due to its long duration and adverse side effect profile and cure rates were low, particularly in those with advanced liver disease (6). However, the development of highly effective direct-acting antiviral agents (DAAs), consisting of an 8-24 week course of well-tolerated oral tablets with > 95% efficacy, has revolutionised HCV treatment (1, 6). Globally, data have convincingly shown that DAAs have been associated with reductions in risk of HCV-related liver failure and HCC (7, 8) and also improved survival and quality of life (9, 10). This led the Australian Government to set national targets for HCV elimination through enhanced testing, linkage to care and treatment with DAAs (11).

Due to the escalating morbidity and mortality burden from HCV in Australia, on March 31st 2016 the Australian and New Zealand Governments introduced universal access to funded DAAs for all people living with HCV infection (12, 13). The impact of these treatments on the lives of Australasians cannot be overstated: prior to 2016, approximately 233,000 Australians and 50,000 New Zealanders were infected; by December 2019, only an estimated 128,000 people remain infected. In Australia 82,000 people with HCV have been treated with DAAs, equating to approximately 44% of the overall estimated infected population (14).

Similarly, in New Zealand 10,000 people with HCV have been treated with DAAs since 2016, equating to approximately 25% of the overall estimated population infected. Limited compassionate access to DAAs for patients with HCV on the waiting list for liver transplantation was available in Australia and New Zealand from 2015, however this was only for select patients with MELD score 15 or greater (15).

Despite compelling data on the number of people cured of HCV, the impact of DAAs on HCV-related liver morbidity and mortality is less well described. Using data from the Australia and New Zealand Liver and Intestinal Transplant Registry (ANZLITR), we describe the impact of introduction of universal access to DAAs on the number and proportion of adult liver transplants being performed for HCV-related liver disease and HCC, and survival post liver transplant, as surrogate markers of reductions in HCV-related disease burden in Australia and New Zealand.

Methods

Complete de-identified data for all adult liver transplants performed within the ANZ LITR database collected between 1st January 1990 and 31st December 2019 was used for this study. Variables included date of transplantation, liver disease aetiology, age and biological gender. Wait list data were also available from 1st January, 2004 to 31st December, 2020. Wait list data included date of listing, indication for liver transplantation and outcome (transplantation, death, delisting and reason for delisting). In the ANZLITR all liver transplants have up to four underlying liver disease aetiologies listed; all adult (16 years and older) liver transplants with HCV recorded as a primary, secondary, tertiary or quaternary indication for transplantation in the dataset were included as HCV cases. HCV case ascertainment included first and subsequent liver transplants for HCV-related liver failure, HCV related HCC, and where HCV was not the sole cause of liver disease (for example, HCV and alcohol related liver disease). In Australia and New Zealand, HCV testing became available from 1990. Universal access to DAAs was introduced in Australia on March 31st, 2016 and later in 2016 in New Zealand.

Discrete data were described using number (proportion) and continuous data by mean and standard deviation (normally distributed) or median (IQR) for non-parametric data. Year of

transplant was divided into 5-year eras (Era 1 1990-1994, Era 2 1995-1999, Era 3 2000-2004, Era 4 2005-2009, Era 5 2010-2014 and Era 6 2015-2019). Proportions were compared using Chi square test. To explore the impact of universal access to DAAs on the number of adult liver transplants performed for HCV per year, we performed an interrupted time series regression analysis (16), where we compared the rate of hepatitis C-related liver transplants (mean number of hepatitis C related liver transplants per year) before and after introduction of DAAs, with the point of interruption defined as March 2016 when universal access to DAAs was introduced for HCV in Australia and New Zealand. Trends in wait-listing patients for liver transplantation and delisting for clinical improvement were also described by HCV status. Cox proportional hazards modelling was used to determine the impact of DAAs on survival post-transplant, adjusted for age category and HCC diagnosis.

This project was approved by the ANZLITR steering committee and institutional ethics committee (Austin Health HREC, Project number 64438) with a waiver of consent.

Results

Between 1st January 1990 and 31st December 2019, 5318 adult liver transplants were performed. Of these, 346 (7%) were repeat liver transplants. The number of adult liver transplants performed per annum steadily increased annually from 54 in 1990 to 311 in 2019, equating to a mean increase of 9.5 adult liver transplants performed per year (95% CI 9.4-9.6, adjusted R^2 0.9, $p<0.001$).

During the study period, 1531 (29%) of adult liver transplants were performed for HCV; 193 in New Zealand and 1338 in Australia; 35 (2%) were re-transplants for recurrent hepatitis C. The number of adult liver transplants for HCV steadily increased from 5 in 1990 to 97 in 2016, then fell to 73 in 2019 (**Figure 1)**. Similarly, the proportion of liver transplants performed for HCV increased from 9% in 1990 to 39% in 2012, remained steady between 2012-2014, then fell to 23% in 2019 (**Supplementary Figure 1).** Linear regression modelling showed that prior to introduction of DAAs, across the 1990-2015 time-period there was a significant mean increase of 3.5 adult liver transplants performed for HCV per year. However, between 2016 to 2019 there was a significant mean decrease of 7.9 adult liver transplants per year for HCV ($p<0.001$) (**Figure 2**).

HCV is the most common liver disease aetiology among adults receiving liver transplant for HCC, accounting for 718 of 1,331 (54%) of HCC-related liver transplants performed during the study period. The number of adult liver transplants performed for HCC per year (of all causes) increased steadily from 1995 at a mean rate increase of 3 HCC-related transplants per year to a peak of 105 liver transplants in 2016, then fell by a mean rate reduction of 2 HCC transplants per year to 98 liver transplants in 2019; interrupted time series analysis confirmed this was a significant change in mean HCC-related liver transplant rate per year after introduction of DAAs in 2016 compared with the mean HCC liver transplant rate per year between 1990-2016 ($p<0.001$). This appeared to be driven by the more sizeable decrease in liver transplants for HCV-related HCC from 65 in 2016 to 50 in 2019 (**Figure 3)**: interrupted time series analysis confirmed a significant reduction in the rate of HCV-related HCC liver transplants performed after introduction of DAAs ($p<0.001$) - prior to DAAs, across the 1990-2015 time-period there was a mean increase of 2 adult liver transplants performed for HCV-related HCC per year. However, post the introduction of DAAs there was a mean decrease of five adult liver transplants for HCV-related HCC per year ($p<0.001$; **Figure 4**).

Wait list data for patients listed for liver transplantation in Australia and New Zealand were available from January 1, 2004 to December 31, 2020. Since January 1, 2004 there were 6,148 wait-listings for liver transplantation in 5,247 individuals. Of these, 3962 (76%) were transplanted, 319 (6%) died waiting for a transplant, 194 (4%) became too sick, 211 (4%) had HCC progression outside of transplant criteria, 256 (5%) patients clinically improved and no longer required a transplant and 305 (6%) were delisted for other reasons (including temporary delisting).

Figure 5A shows the number of patients waitlisted for liver transplantation per year. There was a significant fall in the number and proportion of patients listed for liver transplantation per year ($p<0.001$), with a decline in HCV patients listed for liver transplantation since 2016 compared to those waitlisted for liver transplantation for other liver diseases. The number of patients wait listed for liver transplant who were delisted due to clinical improvement are shown in **Figure 5B**. Overall, there was no significant difference in the number or proportion of patients removed from the liver transplant wait list over time when stratified by HCV status. Among those with HCV who were waitlisted for liver transplant, the proportion with HCC increased steadily over time from 4% in Era 1 to 71% in Era 6 after introduction of

DAAs, despite an overall fall the the number of people with HCV waitlisted for transplant after 2016.

Finally, we explored whether DAAs have impacted upon post liver transplant survival among adults who received their first liver transplant for HCV (n=1,488, **Table 1**). Although recipients of liver transplants for HCV were significantly older after 2016 (introduction of DAAs) compared with prior years (χ^2 p<0.001), age category was not associated with post-transplant patient survival. There was evidence of a cohort effect, with the proportion of liver transplants performed for HCV in older individuals relative to younger individuals increasing by Era (χ^2 p<0.001) compared to recipients of liver transplant for other indications (**Supplementary Figure 3** and **Supplementary Table 1)**. The Kaplan-Meier survival curve in **Figure 6** shows the survival curve post DAA introduction (2016-2019) separates from the survival curve pre- introduction of DAAs (1990-2015) in HCV patients undergoing liver transplantation, Log-Rank p-value <0.001. Though the follow up duration after introduction of DAAs is relatively short, introduction of DAAs was associated with a 31% reduction in death after liver transplantation when adjusted for age category at transplant and presence of HCC (HR 0.7, 95% CI 0.5-1.0, p=0.05; **Table 1**).

Survival post liver transplant has improved over time (3, 4), however strong collinearity between of introduction of DAAs and era prevented model adjustment for era; because introduction of DAAs was defined by year (2016) and the post-DAA period coincided exactly with the 2015-2020 era, both variables could not independently predict the dependent outcome of interest and could not therefore be both included in the same regression model. The Kaplan-Meier curves (**Figure 5**) show improved survival for all adult liver transplant recipients since 2016, including those without HCV. However, among people transplanted between 2015-2019 there was no relationship between survival and year of transplant when adjusted for HCV status (adjusted HR 0.9, 95% CI 0.8-1.0, p=0.2).

Discussion

The ANZLITR data show the introduction of universal access to DAAs in Australia and New Zealand in 2016 is associated with a reduction in the number and proportion of adult liver transplants performed for HCV. The decreasing requirement for transplantation for HCV

after 2016 is a surrogate marker for the impact of DAAs on HCV -related liver disease and HCC more broadly. Prior to 2016, the annual number and proportion of liver transplants performed for HCV steadily increased, however from 2016 there was a significant decline in the HCV-related liver transplantation rate.

For many years HCV has been the leading indication for liver transplantation due to cirrhosis and HCC (3). However, introduction of curative DAAs that preserve liver function and halt progression of liver cirrhosis has led to a 16% reduction in the number of people in Australia and New Zealand receiving liver transplantation for HCV-related liver cirrhosis. This early reduction in HCV transplants is likely due to successful rescue of early decompensation with DAAs and prioritisation of compensated cirrhotics for treatment in the initial years of DAA availability. A similar observation has been reported from transplant centres outside of Australasia (17-22). In 2018, the European Liver and Intestinal Transplant Association (ELITA)(18) reported a greater than 50% reduction in the proportion of liver transplants performed for HCV after local DAA availability from 2013. The greater number of transplants prevented in Europe compared with Australia may reflect earlier DAA availability through trials and compassionate access programs since 2013 and longer duration of follow up (five years, compared with three years in our study). Similar benefits of DAAs have been reported in the USA (20-22). Although changes in the number of adults requiring liver transplantation for other aetiologies such as non-alcohol-related fatty liver disease may have played a role in the decrease in proportion of liver transplants for HCV since 2016 (4), this factor is unlikely to be the only explanation for the significant decline in HCV related liver transplants (22).

Key evidence of the impact of DAAs on hepatitis C related liver transplantation is also provided by our wait list data analysis, which shows a significant reduction in the number and proportion of people with HCV who were wait listed for liver transplantation after introduction of DAAs in 2016 compared to other indications for transplant. ELITA data also showed that DAAs facilitated delisting of people with HCV awaiting transplantation due to improved liver function (19). We did not observe a significant increase in the number of HCV patients who were delisted due to clinical improvement after availability of DAAs in our dataset, which may reflect the higher MELD scores among Australian and New Zealand patients compared with those in European centres. From 2014, waitlisted patients with MELD scores > 15 were routinely treated with DAAs in Australia and New Zealand (15).

However, we have previously shown that a significant proportion of those with MELD scores > 20 who were treated in Australia and New Zealand still required liver transplantation (15). This is in contrast to European centres, where data reported by Belli and colleagues from the ELITA registry showed among those treated with DAAs who were waitlisted for transplant, 50% had a MELD score < 16 and 39% had a MELD score < 20(19). In addition, in Australia and New Zealand after 2016, universal access to DAAs meant most patients with hepatitis C were already cured by the time they were listed for transplant, therefore the number expected to clinically improve to the point of delisting was very small. Another potential reason there was not a significant change in the number of people with HCV delisted for clinical improvement after universal access to DAAs is that the proportion of HCV patients listed for transplantation who also had HCC increased over time, peaking at 71% in the era when universal access to DAAs became available (2015-2019). People waitlisted for liver transplant who also have HCC are more likely to remain on the wait list after DAA treatment than those without HCC even if their liver function improves, which may also contribute to explain the non-significant impact of DAAs on delisting due to clinical improvement.

Our data also show that after 2016 there was a significant decrease in the annual rate of liver transplants performed for HCC ($p<0.001$), predominantly driven by a reduction in HCV-related HCC liver transplant rate ($p<0.001$). In Australia, HCV is the leading cause of HCC (23, 24) and DAA treatment is expected to reduce the incidence of HCV-related HCC as has been shown overseas (7, 8). However, as most people who develop HCC with HCV infection have established cirrhosis, the impact of DAAs on HCC incidence is likely to continue to be observed over the next 5-10 years (25). The reduction in the number of liver transplants performed for HCV-related HCC seen in our study may be due initially to DAA treatment - induced improvements in liver function, which allows a greater number of patients to access curative treatment options other than transplantation (15). Prior to DAAs, many people with HCV-related HCC also had decompensated liver disease and were not suitable for first-line interferon-based treatments for HCC that require preserved liver synthetic function. Liver transplantation is the treatment mode of choice for HCC when underlying liver function is poor, but the tumour is early stage (26). However, with improved liver function due to DAA treatment, a greater number of people with HCV-related HCC would potentially be suitable for other HCC curative treatments such as surgical resection or ablation. DAA-induced sustained virological response (SVR) is predicted to contribute to a decrease in HCC incidence in patients with HCV-related cirrhosis (8). The relative contribution of DAA induced SVR to the reduction in number of liver transplants for HCV-related HCC in our

dataset is likely to be less than the impact of improved liver function post SVR given the relatively short follow up time period of three years. Our data clearly show a cohort effect for HCV-related liver transplantation, with a steady increase in the proportion of HCV-related liver transplants performed in older age categories over time. We observed a sharp decline in HCV-related HCC from 2016 onwards, despite increasing age of liver transplant recipients, further suggesting an impact of DAAs on treatment outcomes amongst people living with HCV in Australia.

Prior to the introduction of DAAs, donor organ re-infection with HCV was universal after liver transplantation(1, 2). However, data show DAAs effectively treat graft reinfection, thereby reducing the need for re-transplantation for aggressive HCV recurrence and improving post-transplant survival (27-29). In our dataset, only 35 (2%) of all adult liver transplants were for recurrent HCV. Our data describing the impact of DAAs on survival after HCV-liver transplantation is limited by the short three-year duration of follow up after 2016, however our data suggest an emerging benefit on post-transplant survival among people living with HCV transplanted during the DAA era. This observation is echoed by European and North American data which show a 13% improvement in survival after availability of DAAs (18), including early post-transplant survival (29, 30). Though post liver transplant survival has continually improved over time due to refinements in surgical techniques and improved immunosuppression management (3), there have been no major changes to liver transplantation protocols in Australia and New Zealand during the last three years that would account for the improvement in survival seen in HCV-related liver transplant recipients after the introduction of DAAs. In our study, we could not include Era or Year post transplant in our Cox proportional hazards model due to strong collinearity with year of introduction of DAAs. However, we did show that there was no association between year post transplant and survival when the dataset was restricted to adults transplanted between 2015-2019. In addition, improvements in post transplant survival over time are most pronounced in the first year post transplant, but have minimal impact beyond the first year post transplant (31). Taken together, these data suggest but do not confirm that the improvement in HCV liver transplant recipient survival after 2016 is more likely due to introduction of DAAs, rather than a time post-transplant effect.

Our study has several limitations. Firstly, the ANZLITR collects limited demographic and clinical data. DAA treatment data were unavailable for individual liver transplant recipients;

however, since 2016 it has been common practice at liver transplant centres across Australia to use DAAs to treat HCV patients awaiting liver transplantation through Medicare-funded universal access to DAAs and since this time most patients listed for transplantation with HCV as the primary indication are in fact cured of HCV (32). A proportion of HCV patients with MELD scores of 15 or greater received DAAs from 2014-2015 through clinical trials and compassionate access programs whilst on the waiting list prior to universal DAA access (15). This information is not captured in our analysis. Similarly, investigation of potential confounding and interacting factors was limited to variables available in the ANZLITR dataset, however key drivers of mortality post-transplant including liver disease aetiology, presence of HCC and age at transplantation were captured. However, the ANZLITR dataset are the most accurate data to determine the impact of DAAs on liver transplantation in Australia and New Zealand, including the impact on hepatitis C patient waitlisting. An additional consideration is that our samples size is small compared to national datasets in Europe and North America due to the smaller population size in Australia and New Zealand; this may theoretically have introduced the risk of a type I error. Finally, the time of follow up after introduction of universal access to DAAs in Australia to date is short, which reduces study power to explore the impact of DAAs on survival post transplant. However, the trends we describe in HCV-related transplant rate and survival are supported by data published internationally.

Conclusion

Introduction of universal access to DAA therapy has been associated with a reduction in the number of liver transplants being performed for HCV and HCV-related liver cancer and has diminished the number of people waitlisted with hepatitis C and deaths related to HCV post transplant in Australasia. As more people are cured of HCV prior to the development of cirrhosis, it is likely that we will continue to observe further decrease in numbers of HCV-related adult liver transplants. Sustained investment in universal access to DAAs is an important measure to reduce HCV-related morbidity and mortality worldwide.

Acknowledgements

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Table 1. Association between introduction of universal access to DAAs and mortality post liver transplant in adults with HCV infection: Unadjusted and adjusted Cox proportional hazards analysis (n=1,488, first transplants only)

Variable	Crude HR	95% CI	p-value	Adjusted HR	95% CI	p-value
DAA	0.78	0.55-1.12	0.18	0.69	0.48-0.99	**0.04**
Age Category						
16-29 years	1.00			1.00		
30-39 years	1.47	0.33-6.51	0.61	1.46	0.33-6.48	0.62
40-49 years	2.00	0.48-8.33	0.34	1.96	0.47-8.15	0.36
50-59 years	1.91	0.46-7.90	0.37	1.85	0.44-7.69	0.40
60-69 years	2.64	0.63-11.07	0.19	2.67	0.63-11.30	0.18
>=70 years*	-			-		
HCC	1.12	0.93-1.35	0.24	1.09	0.89-1.34	0.39

*Very small number of subjects, therefore excluded from analysis

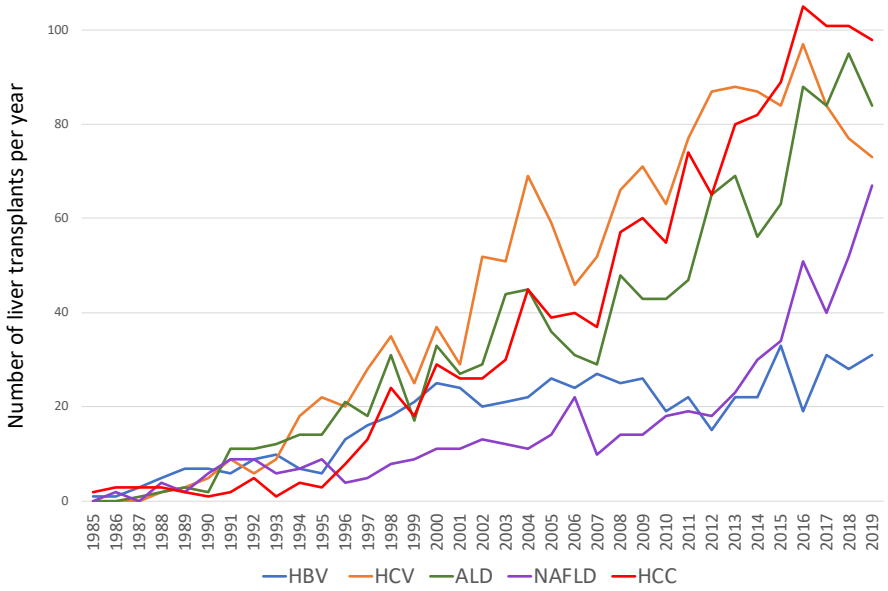

Figure 1. Number of adult liver transplants performed per year between 1985 and 2019, stratified by aetiology (n=5460. Hepatitis C (HCV) cases include HCV-related liver failure and HCV-related hepatocellular carcinoma (HCC). Diagnostic categories are non-exclusive.

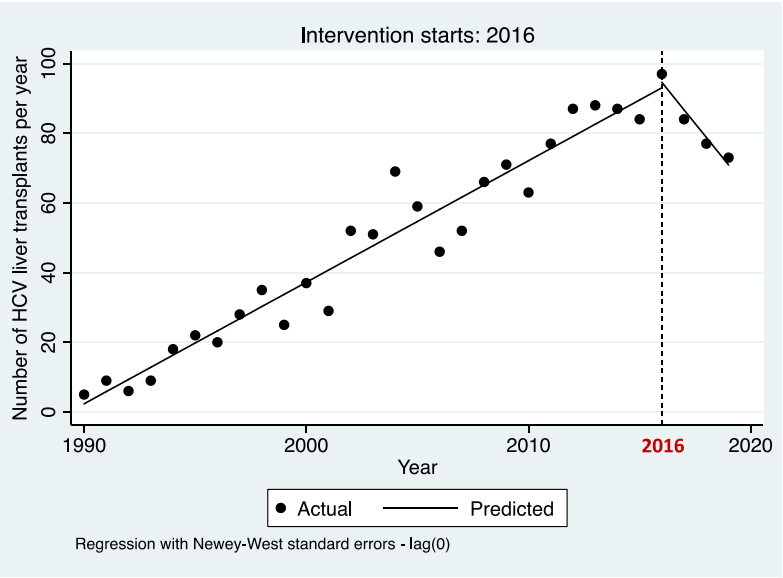

Figure 2. Interrupted time series analysis of the impact of universal access to DAAs in 2016 on the number of liver transplants performed for hepatitis C (HCV) per year, including both HCV-related liver failure and HCV-related HCC cases ($p<0.001$).

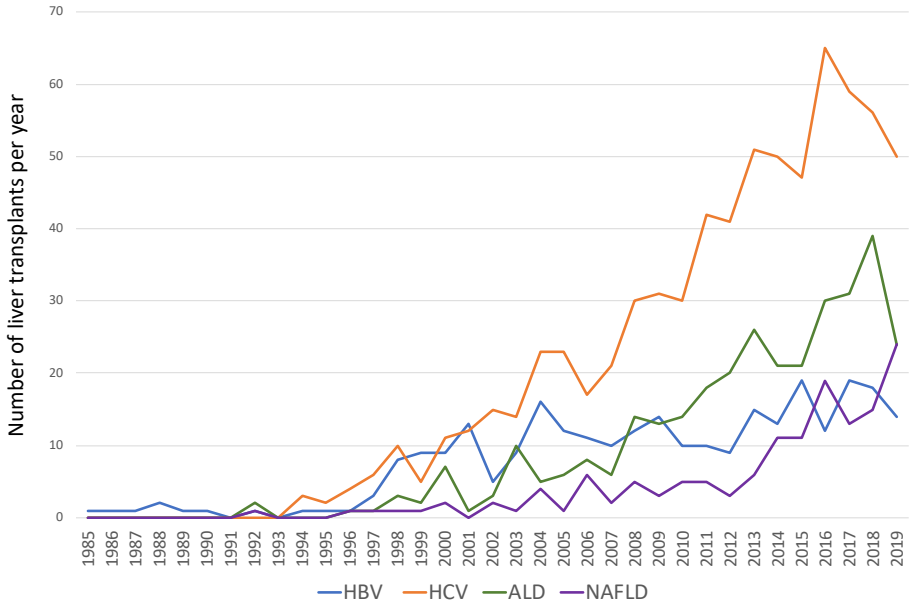

Figure 3. Number of adult liver transplants performed for HCC per year, stratified by underlying aetiology (n=1331). Aetiology categories are non-exclusive.

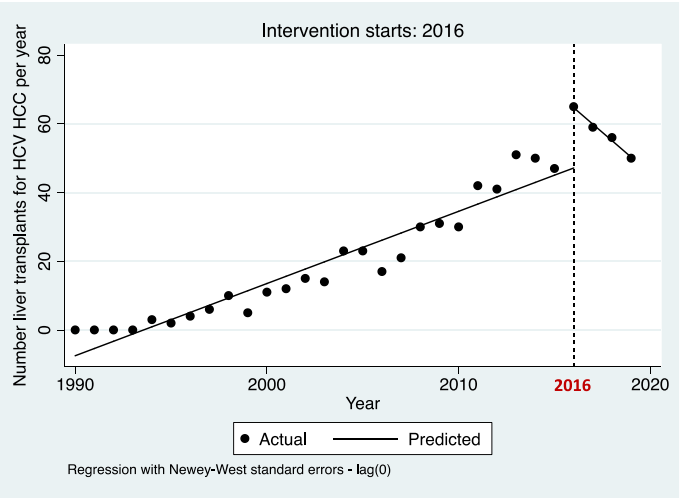

Figure 4. Interrupted time series analysis of the impact of universal access to DAAs in 2016 on the number of liver transplants performed for hepatitis C-related HCC per year (p<0.001).

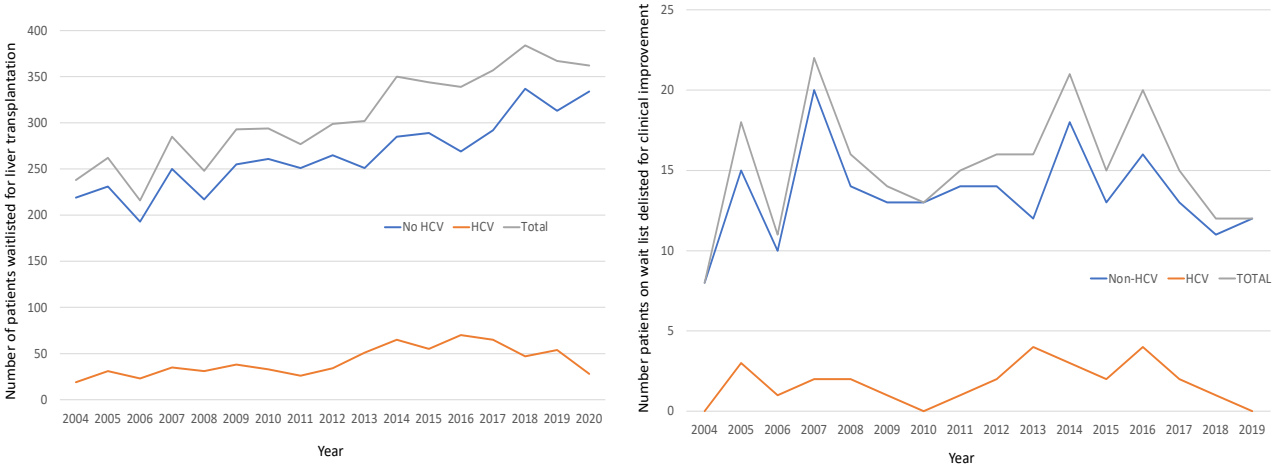

Figure 5. A. Number of patients waitlisted for liver transplant per year, stratified by hepatitis C status (p<0.001). **B.** Number of patients delisted for liver transplant due to clinical improvement, stratified by HCV status (p=0.89).

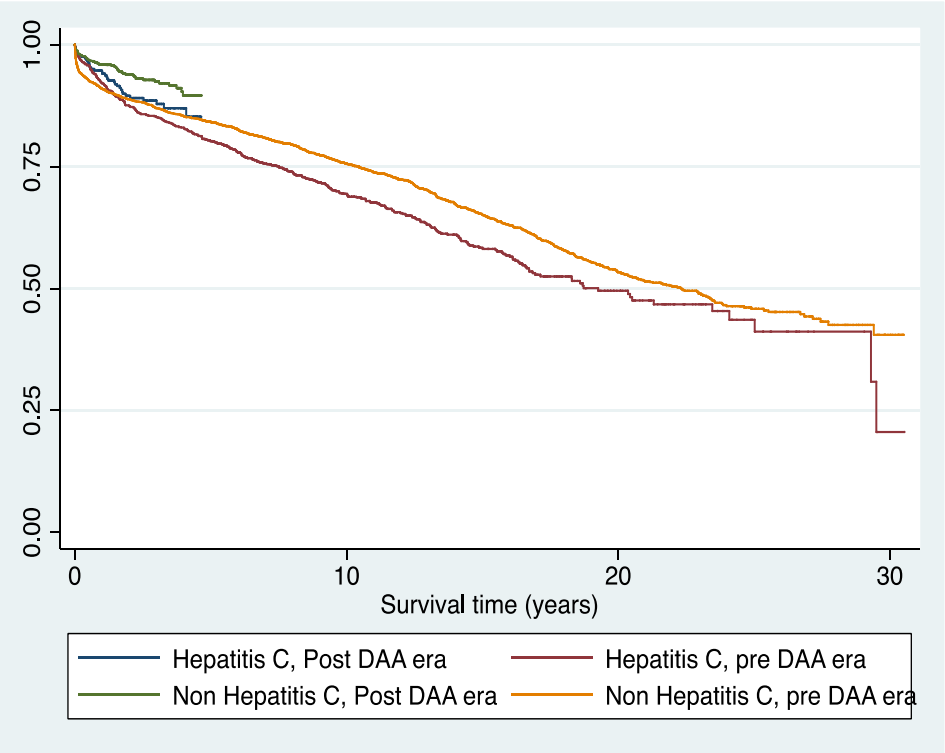

Figure 6. Kaplan-Meier survival curves post liver transplant for adults with chronic hepatitis C infection pre and post DAA availability (Log-Rank p<0.001). Time period of analysis 1990-2019.

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