The increasing burden of potentially preventable liver disease among adult liver transplant recipients: A comparative analysis of liver transplant indication by era in Australia and New Zealand

J Howell1,2,3,4, G Balderson5, M Hellard3, PJ Gow1,2, SI Strasser6, KA Stuart7, A Wigg8, G Jeffrey9, E Gane10, PW Angus1,2.

Liver Transplant Unit, Austin Hospital, Melbourne1; Department of Medicine, University of Melbourne2; Centre for Population Health, MacFarlane-Burnet Institute, Melbourne, Australia3; Department of Medicine, Imperial College, London, UK4; Australia & New Zealand Liver Transplant Registry, Princess Alexandra Hospital, Brisbane, Australia; A W Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, Australia6; Queensland Liver Transplant Unit, Princess Alexandra Hospital, Brisbane, Australia7; South Australian Liver Transplant Unit, Flinders Medical Centre, Adelaide, Australia8; West Australian Liver Transplant Unit, Charles Gardiner Hospital, Perth, Australia9; New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand10.

Corresponding author: Dr Jessica Howell
Department of Medicine
Level 10, QEQM Building, St Mary’s Hospital
South Wharf Rd, London W2 1NY
jhowell@imperial.ac.uk
phone: 020 3312 6666

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Abstract

Background: Hepatitis C (HCV), hepatitis B (HBV), alcohol-related liver disease (ALD) and non-alcohol-related fatty liver disease (NAFLD) are leading indications for adult liver transplantation in Australia and New Zealand. However, these diseases are potentially preventable through effective primary and/or secondary prevention strategies. This study evaluates the relative contribution of potentially preventable liver diseases to liver transplant numbers in Australia and New Zealand over time.

Methods: Prospectively recorded clinical, demographic and outcome data were collected from the Australian and New Zealand Liver Transplant Registry for all primary adult liver transplants performed in Australia and New Zealand from January 1, 1985 until December 31, 2012. Potentially preventable liver disease was defined as HBV, HCV, NAFLD, ALD and HCC. The aetiology of liver disease leading to liver transplantation and the proportion of preventable liver disease-related liver transplantation was compared between Era 1 (1985-1993), Era 2 (1994-2003) and Era 3 (2004-2012).
Results: Overall, 1252 of 3266 adult primary liver transplants (38.3%) were performed for potentially preventable liver disease. There was a significant increase in the proportion of liver transplants due to preventable liver disease from 21.2% (93 of 439) in Era 1, to 49.8% (623 of 1252) in Era 2 and 63.5% (1000 of 1575) in Era 3 (p<0.0001). Over time, there was a significant increase in HCV (p<0.0001), ALD (p=0.002) and NAFLD (p<0.0001) as a primary indication for adult liver transplant, whereas HBV has significantly decreased from Era 1 to Era 3 as an indication for transplant (p<0.0001). The number of transplants performed for HCC also increased across Eras (p<0.0001), with 84% due to underlying potentially preventable liver disease.

Conclusion: Since 2004, the majority of primary adult liver transplants within Australia and New Zealand have been due to potentially preventable liver diseases and the prevalence of these diseases has increased over time. This finding represents an opportunity for clinicians to make a significant impact on the overall burden of advanced liver disease in Australia and New Zealand by improving primary and secondary prevention measures.
Liver transplantation is a highly effective treatment for end-stage liver disease in appropriately selected patients, with excellent long-term survival (1). Globally, the need for liver transplantation is increasing and procuring enough donor organs to cope with this growing demand is an increasing challenge for transplant centres around the world (2, 3).

Within Australia and New Zealand, socio-cultural factors influencing public acceptance of organ donation, an opt-in policy for organ donation, smaller population size and the vast distances between cities present considerable logistical challenges to the availability of transplantation (4). Whilst major efforts are being made to increase donor organ supply, it is logical that these measures should occur in parallel with attempts to lower demand by reducing the burden of end-stage liver disease requiring liver transplantation.

Four of the leading indications for adult liver transplantation in Australia and New Zealand are hepatitis C (HCV), hepatitis B (HBV), alcohol-related liver disease (ALD) and non-alcoholic fatty liver disease and steatohepatitis (NAFLD/ NASH). The demand for transplantation for these diseases could be reduced by means of primary prevention strategies to reduce disease incidence, or secondary screening and treatment strategies to prevent the development of advanced liver disease in affected patients. Therefore, every patient requiring a liver transplant for one of these potentially preventable liver diseases represents a limitation of current health prevention policies, case identification and effective treatment strategies.

Hepatocellular carcinoma is also a major indication for liver transplantation. The vast majority of HCC occurs in patients with established cirrhosis. A marked reduction in HCC risk is potentially achievable through effective treatment of chronic liver diseases to prevent the development of cirrhosis (5). HCC can therefore be considered as a potentially preventable indication for liver transplantation.
The rising physical, personal and economic costs to patients and the health-care resource burden of potentially preventable liver disease is therefore a major public health concern. However, there is little data outlining the contribution of these diseases to liver transplantation demand in Australia and New Zealand. This study examines the number and proportion of liver transplants performed for potentially preventable liver diseases over time within Australia and New Zealand from 1985 to 2012, focusing on HCV, HBV, NAFLD and ALD. Data describing the transplant burden due to HCC and the proportion of HCC cases related to preventable liver diseases are also presented. Finally, possible measures to reduce the burden of potentially preventable liver disease are discussed.

Methods

This study included all adult patients over 16 years of age who received a primary liver transplant between 1st January, 1985 and 31st December, 2012 inclusive of all liver transplant centres within Australia (Sydney, Melbourne, Brisbane, Perth, Adelaide) and New Zealand (Auckland). Transplanted livers included cadaveric, living donor and split grafts. Liver transplant waitlist data (including the number of patients awaiting liver transplant and the outcomes of those waitlisted) and liver transplant patient demographics, primary indication (defined as the leading cause of end-stage liver disease, as classified by the treating transplant physician team) and outcome data were obtained from the Australian and New Zealand Liver Transplant Registry, which collates all cumulative data on liver transplantation from all six liver transplant centres within Australia and New Zealand (Source: 24th Report of the Australia and New Zealand Liver Transplant Registry, 2012; www.anzltr.org; accessed April 24, 2014). Data is complete and has been entered prospectively from the first liver transplant
performed in 1985 until the present. For this study, all data from January 1, 1985 until December 31, 2012 were included. Data was divided into three Eras: Era 1 (1985-1993), Era 2 (1994-2003) and Era 3 (2004-2012) for analysis.

The primary indication for liver transplantation was used to classify whether the liver disease was potentially preventable or non-preventable. The proportion of patients undergoing liver transplantation for potentially preventable liver disease was then compared with non-preventable liver disease. Potentially preventable liver diseases were defined as conditions that could be effectively prevented through evidence-based primary or secondary prevention strategies. These liver diseases were HCV, HBV, NAFLD and ALD. HCC was also classified as a preventable cause of liver transplantation for the reasons outlined previously. The proportion of potentially preventable liver disease-related liver transplantation was measured by year and comparisons were made between Era 1 (1985-1993), Era 2 (1994-2003) and Era 3 (2004-2012).

**Statistical Analysis**

Statistical analysis was performed using SPPS (SPSS Inc, Version 19 software, Chicago, IL, USA) and Prism 5.0c for Macintosh software (Graphpad Software Inc, La Jolla, CA, USA). Categorical data were compared using chi-square for equal proportion and presented as numbers (%). Continuous normally distributed data were compared using Student t-test (two categories) or ANOVA with Bonferroni correction (multiple categories) and reported as mean +/- standard error of the mean. Non-normally distributed variables were compared using Mann-Whitney U test (two categories) or Kruskall-Wallis test (multiple categories)
with Dunn’s test for multiple comparisons and presented as median (interquartile range). A two-sided p-value of 0.05 was considered to be statistically significant.

Results

From 1st January 1985 until 31st December 2012, 3266 adult patients underwent primary orthotopic liver transplantation, with the highest annual number of 202 recorded for 2012. Of 3490 cadaveric liver transplants performed in 3266 recipients, 245 (7%) were reduced size grafts (203 split grafts, 13 living donor grafts and 29 other reduced size grafts), one patient received a whole liver domino transplant and 14 received adult living donor transplants.

There was a steady increase in the annual number of adult patients receiving a liver transplant, rising from four in 1985 to 202 in 2012 and a significantly greater number of adult patients receiving liver transplants in Era 3 (1575 liver transplant recipients) compared with Eras 1 (439 liver transplant recipients) and Era 2 (1252 liver transplant recipients, p<0.0001).

In the last 5 years, the number of adult patients on the liver transplant waitlist increased from 489 patients in 2008 to 539 in 2012. Over this period 45-50% of those on the waiting list received a transplant each year. The number of patients removed from the waiting list due to death, tumour progression beyond transplant criteria or becoming too unwell for transplant has remained stable over time (14% in 2008 and 11% in 2012).

The number of adult liver transplants performed for the primary indication of potentially preventable liver disease (HCV, HBV, ALD or NAFLD) increased over time from two of four (50%) in 1985 to 137 of 202 (67.8%) transplants in 2012. There was a significant increase in the proportion of liver transplants due to preventable liver disease from 93 of 439
(21.2%) in Era 1 to 623 of 1252 (49.8%) in Era 2 (p<0.0001, OR 1.77, 95% CI 1.57-2.04) and to 1000 of 1575 (63.5%) in Era 3 (p<0.0001, OR 3.69, 95% CI 2.86-4.75) as outlined in Figure 1.

Over time, the number of adult liver transplants performed annually for HCV, NAFLD and ALD has increased, whilst those for HBV have decreased (Figure 2). There was a significant increase in HCV as a primary indication for liver transplant over time, from 21 of 439 primary transplants (4.8%) in Era 1 to 274 of 1252 (21.9%) in Era 2 (p<0.0001, OR 1.58, 95% CI 1.326-1.885) and 474 of 1575 (30.1%) in Era 3 (p<0.0001, OR 1.54, 95% CI 1.294-1.825). Overall, HCV infection was the most common primary indication for adult liver transplantation, accounting for 22.4% of all adult liver transplants performed in Australia and New Zealand (769 of 3266 primary liver transplants).

There was a significant increase in the proportion of liver transplants performed for ALD over time: 7.2% (32 of 439) transplants in Era 1 were performed for a primary indication of ALD, compared with 13.8% (173 of 1252) in Era 2 and 12.6% (198 of 1575) in Era 3 (p=0.002). However, whilst the difference between Eras 1 and 2 was significant (p=0.0004), the difference between Eras 2 and 3 was not (p=0.35), with the proportion of transplants performed for ALD decreasing slightly between Eras 2 and 3. ALD was the second most common primary indication, accounting for 12.5% of all adult liver transplants performed in Australia and New Zealand.

NAFLD and NASH have only emerged as an indication for liver transplantation in Australia and New Zealand since 1998 due to both a lack of recognition and firm diagnostic criteria for NAFLD and NASH prior to this time. However, the number of primary liver transplants
performed for NAFLD-related liver disease and HCC has risen steadily since this time (Table 1). There was a significant increase in the proportion of liver transplants performed for NASH from 0 of 439 (0%) in Era 1, to 8 of 1252 (0.6%) in Era 2 and 75 of 1575 transplants (4.8%) in Era 3 (p<0.0001). Overall, 83 of 3266 (2.5%) primary liver transplants were performed for a primary diagnosis of NAFLD or NASH during the study period.

In contrast, the proportion of liver transplants performed for a primary indication of HBV-related liver disease fell over time, from 30 of 439 (32.3%) in Era 1 to 107 of 1252 (17.2%) in Era 2 and 66 of 1575 (6.6%) in Era 3 (p<0.0001). Overall, HBV accounted for 6.2% (203 of 3266) of all primary liver transplants over the study period. HBV also accounted for 23% (72 of 311) of transplants for fulminant liver failure during the entire study period.

Since 1985, 685 adult liver transplant recipients had HCC either as a primary diagnosis (259, 37.8%) or secondary diagnosis (including incidental finding on explant) (426, 62.2%). The annual number of liver transplants for which HCC was the primary indication has increased from 2.3% (10 of 439) in Era 1 to 4.9% (61 of 1252) in Era 2 (p=0.03) and to 11.9% (187 of 1575) in Era 3 (p<0.0001).

Overall, 84% of HCC cases were due to potentially preventable liver disease (575 of 685 HCC cases), with chronic viral hepatitis accounting for 68% of preventable liver disease-related HCC. HCV was the most common underlying aetiology (308 of 685 HCC cases, 45%), with HBV accounting for 21% (144 of 685) and HCV/ HBV +/- HDV co-infection accounting for 2% (14 of 685). ALD accounted for 13% (89 of 685) and NAFLD/ NASH accounted for 3% of HCC cases (21 of 685).
Discussion

These data show that the overall demand for liver transplantation in Australia and New Zealand is increasing (Figure 1). Only half of the adults on the liver transplant waitlist were transplanted, with an attrition rate of 10% per year, usually due to disease progression or death (Figure 3). From a public health perspective, it is therefore concerning that the burden of potentially preventable liver disease requiring transplantation is increasing and this represents a general failure in current health policy, screening and treatment programs to protect patients from advanced liver disease.

HCV was the most common primary indication for adult liver transplantation overall (22.4%) and the proportion of transplants performed for HCV significantly increased over time. Though it should be noted that HCV testing was not widely available prior to 1991, which contributes to the lower number of reported cases of HCV in Era 1, these findings are mirrored by similar trends in the USA and Europe (6-9). With over 185 million people estimated to be infected with HCV worldwide, HCV-related cirrhosis and HCC represents a major global public health problem (Source: WHO Guidelines for the screening, care and treatment of persons with hepatitis C infection. http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1; accessed November 24, 2014).

There are a number of effective primary prevention strategies to reduce the spread of HCV infection, but these are under-utilised. Injecting drug use is the primary mode of HCV transmission in Australia and New Zealand (10) and needle and syringe exchange programs and opioid substitution therapy have proven efficacy for HCV primary prevention amongst
people who inject drugs (11-14) (Source: Return on Investment of Needle and Exchange Programs in Australia: Summary Report. http://www.health.gov.au/internet/main/publishing.nsf/Content/9610691C9FBD7966CA257F0001E37EF/$File/roisum.pdf; accessed November 24, 2014). However, current coverage of these programs is inadequate to fully prevent HCV transmission. HIV positive men who have sex with men are also at increased risk of HCV through sexual transmission and education programs in this group are required, particularly as HCV progresses more rapidly in this subgroup (15). Strict implementation of national health policies to reduce iatrogenic spread through medical and surgical procedures, acupuncture and tattooing is also vital(8). However, it will take many years for primary preventative strategies to influence the current burden of HCV related disease. These measures also do not reduce HCV prevalence in other high-risk groups, such as immigrants from HCV endemic countries.

Cost-effective HCV treatment is available for the majority of patients if treated prior to the development of significant liver disease (8, 10). Importantly, the new highly active direct-acting antivirals (DAAs) are more efficacious across all HCV genotypes, require shorter treatment duration and have fewer side effects than interferon-based treatment regimens (18-20). With DAAs, it is now possible to cure HCV in the vast majority of patients, avoiding progression to cirrhosis and the development of HCC. Furthermore, the data demonstrate that many of the DAAs can be used safely in patients with advanced liver disease who are unsuitable for standard interferon-based antiviral therapy(20-22). Based on the experience following the introduction of the oral antiviral agents for HBV(23-26), it is anticipated that effective treatment of patients with HCV–related advanced cirrhosis will lead to improvements in liver function which are sufficient to obviate the need for liver transplantation in a significant proportion of patients. However, screening of at-risk
individuals and treating those infected remain the rate-limiting steps to reduce viral transmission among at-risk individuals and decrease the burden of HCV-related liver disease (16, 17).

ALD was the second most common potentially preventable indication for liver transplantation (12.5%) and the proportion of liver transplants performed for ALD increased over time. Globally, ALD is responsible for a significant health burden and is a major indication for liver transplantation (27). Globally, ALD prevalence varies considerably between countries, reflecting the local accessibility, affordability and cultural context of alcohol use (27). A key factor in the variation in ALD-related disease burden is national health policy (29).

Screening and treatment strategies exist for secondary prevention of ALD, but remain under-utilised. Disappointingly, a recent study showed that the prior alcohol history was documented in less than 25% of patients referred to an Australian liver disease clinic, suggesting there may a general failure to properly screen for alcohol abuse (31). The 10-point Alcohol Use Disorders Identification Test (AUDIT) is an effective screening test to determine those at risk of alcohol dependence, however this does not predict their risk of liver disease and more specific tests to screen for ALD are needed (27, 32). Support groups and brief interventions in combination with anti-craving medications, such as baclofen, acamprosate and naltrexone, have reported efficacy for reducing alcohol intake (27, 33-37). Unfortunately, current strategies appear only modestly effective (WHO Expert Committee on Problems Related to Alcohol Consumption. Second Report. WHO Technical Report Series 944; http://www.who.int/substance_abuse/expert_committee_alcohol/en/; accessed July 29, 2014) and uptake and continuation of these strategies is suboptimal (27). Importantly, ALD
has been shown to regress with abstinence, thus support and treatment strategies for those already affected by ALD can lead to improvements in liver function and avoid the need for transplantation(27, 38, 39).

There is strong evidence that primary prevention national health policies for reducing alcohol-related harm within the community through reduced access to alcohol-containing products, such as introduction of a minimum cost per unit alcohol and controlled marketing, effectively reduce ALD-related morbidity and mortality (29, 40)(29). This effect is seen rapidly as alcohol-related fatalities tend to reflect recent drinking(30). Further research into more cost-effective and practical strategies to reduce ALD is paramount and a national health policy is likely to be the most effective strategy to reduce ALD in Australia and New Zealand.

Non-alcoholic fatty liver disease (NAFLD) is a burgeoning epidemic in the western world and the most common preventable liver disease worldwide (41), associated with the parallel epidemics of obesity and the metabolic syndrome (42, 43). NAFLD prevalence is also increasing across Asia (44). Current data suggest that three out of every five Australians are overweight or obese (Source: Australian Institute of Health and Welfare, www.aihw.gov.au/overweight-and-obesity/burden-of-disease/; accessed November 23, 2014) and NAFLD is estimated to affect 20-30% of Australians(43). Therefore, NAFLD and its potential consequences of cirrhosis and HCC have become a rapidly emerging global public health concern.

The data presented in this study show that non-alcoholic fatty liver disease (NAFLD) is a rapidly emerging potentially preventable indication for liver transplantation in Australia and
New Zealand. In part, this is due to lack of recognition of the disease entity and conflicting diagnostic criteria prior to the 1990s. Many cases previously labeled as cryptogenic cirrhosis are likely to be unrecognized NAFLD. The increasing rate of NAFLD-related liver transplantation shown in this study mirrors the rapid rise in liver transplantation for this indication in the USA (6, 45-49).

Liver transplantation for advanced NAFLD is often complicated by the presence of significant comorbidities in affected patients including obesity, diabetes, vascular and cardiac disease. Surgery is technically complex in obese patients, with greater blood transfusion requirements and higher rates of infection, deep venous thrombosis, cardiovascular complications and biliary complications. Longer operative times and duration of stay in intensive care post liver transplantation (49, 50) are also reported in NAFLD patients undergoing liver transplantation (51). These increased risks highlight the need to prevent the development of advanced liver disease in patients with NAFLD.

Currently, there is no established medical therapy for NAFLD. Addressing the metabolic syndrome and obesity through diet modification and exercise remains the mainstay for both primary prevention of NAFLD and secondary prevention of advanced liver disease and NAFLD associated HCC (52, 53). More research is needed to explore the cost-effectiveness of primary prevention through national health policies such as improved food labeling, fast food taxation and national health education campaigns. Though a Cochrane review of bariatric surgery in NAFLD in 2010 highlighted the lack of high quality studies (56), evidence suggests bariatric surgery may still prove effective for both primary and secondary prevention of NAFLD in obese patients in (54-56) and benefits for other aspects of the
metabolic syndrome are likely to have an important impact on cardiovascular mortality in NAFLD patients (42).

Pleasingly, there has been a reduction in the contribution of HBV-related liver disease to liver transplantation in Australia and New Zealand over time, which echoes trends in the USA and Europe (6, 7). The combination of an infant vaccination program since 1987 in New Zealand and 1988 in Australia and vaccination of high-risk populations has substantially reduced new HBV infections in Australia and New Zealand (Source: The Australian Immunisation Handbook 2013. 10th Edition: www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home. Retrieved 22 May 2014.) (57, 58). However, there have been no systematic catch-up programs to immunize previously unvaccinated adults and immigrants from HBV endemic countries remain at significant risk of HBV-related advanced liver disease and HCC (57, 59). The reduction in HBV-related liver transplantation also reflects the availability of highly effective drug therapies that control HBV replication, reduce liver injury and prevent or even reverse the progression of liver fibrosis (23, 25, 26).

The data also reflect a shift in the primary indication for transplantation for HBV-related liver disease from cirrhosis to HBV-related HCC. Despite the fall in overall number of transplants for HBV-related chronic liver disease, the number of transplants for HBV-related acute liver failure has remained essentially stable over the study period (23% of fulminant liver failure cases). These cases represent new infections in unvaccinated adults, or flares in patients with HBV cirrhosis who are not on therapy and both scenarios are potentially preventable. It should also be noted that although highly cost-effective treatment is available, patients require screening and appropriate referral to commence antiviral therapy (60, 61). The
majority of patients with HBV infection still remain undiagnosed, or they are not receiving appropriate follow-up (62-64).

In this study, the vast majority of HCC cases were due to potentially preventable liver disease (84%), particularly viral hepatitis. The increase in HCC observed over the duration of the study reflects in part the improvement in surveillance for HCC in cirrhotic patients over the same time period. However, the incidence of HCC is increasing globally and it is now the sixth most common cancer and third most common cause of cancer death worldwide (65, 66). These are sombre statistics when we consider that the majority of HCC are due to potentially preventable liver disease. Primary and secondary prevention of liver disease prior to the development of advanced fibrosis is clearly the most important strategy for reducing the incidence of HCC worldwide.

There are several limitations to our study. The definition of potentially preventable liver disease is arbitrary. Furthermore, NAFLD may not have been recognized as the cause of some cases of cryptogenic cirrhosis, particularly during the early years of liver transplantation in Australia and New Zealand, leading to an underestimate of the disease burden due to this disease. Systematic HCV testing was not available prior to 1991 and this will also have affected the reported number of transplants for HCV in Era 1. However, the study findings are derived from a large, accurate and complete registry dataset of all liver transplant recipients in Australia and New Zealand over the past three decades, making this a strong study design to determine the rising prevalence of potentially preventable liver disease as an indication for liver transplantation over time.
Conclusion

The majority of liver transplants performed in Australia and New Zealand are now due to potentially preventable liver diseases including HCV, ALD, NAFLD and HBV. Potentially preventable liver disease also accounts for the majority of HCC cases both in Australia and New Zealand and worldwide. Improved primary and secondary prevention strategies through screening and early treatment are vital to reduce both the growing physical and socio-economic burden to our patients and national health care resources of potentially preventable liver disease. We are at an exciting crossroad, where changes in national health policies, such as approval of highly effective new direct acting anti-HCV drugs and implementation of proven effective national alcohol reduction policies could substantially reduce the prevalence of advanced liver disease and HCC within Australia and New Zealand. However, a stronger commitment among clinicians and policy makers for urgent action is required to improve patient access to screening and treatment of preventable liver disease in order to reduce the burden of advanced liver disease within our communities.

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Figure 1. Comparison of number of adult primary liver transplants performed for potentially preventable and non-preventable disease indication by Era.

The number of patients receiving a liver transplant for preventable liver disease significantly increased from 93 of 439 (21.2%) in Era 1 to 623 of 1252 (49.8%) in Era 2 (p<0.0001, OR 1.77, 95% CI 1.57-2.04) and to 1000 of 1575 (63.5%) in Era 3 (p<0.0001, OR 3.69, 95% CI 2.86-4.75).
Figure 2. Number of primary adult liver transplants per year by primary diagnosis.
Figure 3. Aetiology of liver disease in adult patients receiving primary liver transplants for HCC.
Acknowledgements

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Table 1. Number of primary adult liver transplants performed for potentially preventable liver diseases by Era.

<table>
<thead>
<tr>
<th>Era</th>
<th>Number Liver Transplants</th>
<th>Number Liver Transplants: Potentially Preventable Liver Disease (%)</th>
<th>Number Liver Transplants: HCV (%)</th>
<th>Number Liver Transplants: HBV (%)</th>
<th>Number Liver Transplants: ALD (%)</th>
<th>Number Liver Transplants: NAFLD (%)</th>
<th>Number Liver Transplants: HCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985-1993</td>
<td>439</td>
<td>93 (21.2%)</td>
<td>21 (4.8%)</td>
<td>30 (6.8%)</td>
<td>32 (7.3%)</td>
<td>0 (0%)</td>
<td>10 (2.3%)</td>
</tr>
<tr>
<td>1994-2003</td>
<td>1252</td>
<td>623 (49.8%)</td>
<td>274 (22.0%)</td>
<td>107 (8.5%)</td>
<td>173 (13.8%)</td>
<td>8 (0.6%)</td>
<td>61 (4.9%)</td>
</tr>
<tr>
<td>2004-2012</td>
<td>1575</td>
<td>1000 (63.5%)</td>
<td>474 (30.1%)</td>
<td>66 (4.2%)</td>
<td>198 (12.6%)</td>
<td>75 (4.8%)</td>
<td>187 (11.9%)</td>
</tr>
</tbody>
</table>

Comparison All Eras (p-value)  
<0.0001  <0.0001  <0.0001  <0.0001  0.0015  <0.0001  <0.0001

Comparison Era 1 to Era 2 (p-value)  
<0.0001  <0.0001  <0.0001  <0.0001  0.0004  0.12  0.028

Comparison Era 2 to Era 3 (p-value)  
<0.0001  <0.0001  <0.0001  <0.0001  0.35  <0.0001  0.0001

Abbreviations: HCV, Hepatitis C virus; HBV, hepatitis B virus; ALD, Alcohol Liver Disease; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma.