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Treatment access is only the first step to hepatitis C elimination: experience of universal antiviral treatment access in Australia

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SUMMARY

Background: Global targets to eliminate hepatitis C (HCV) might be met by sustained treatment uptake. **Aims:** We describe factors facilitating HCV treatment uptake and potential challenges to sustaining treatment levels after universal access to direct acting antivirals (DAA) across Australia.

Methods: We analysed national Pharmaceutical Benefits Scheme data to determine the number of DAA prescriptions commenced before and after universal access from March 2016 to June 2017. We inferred facilitators and barriers to treatment uptake, and challenges that will prevent local and global jurisdictions reaching elimination targets.

Results: In 2016, 32,887 individuals (14% of people living with HCV in Australia) commenced HCV DAA treatment, and 34,952 (15%) individuals commenced treatment in the first year of universal access. Treatment uptake peaked at 13,109 DAA commencements per quarter immediately after universal access, but more than halved (to 5,320 in 2017Q2) within 12 months. General practitioners have written 24% of all prescriptions but with a significantly increased proportion over time (9% in 2016Q1 to 37% in 2017Q2). In contrast, hepatology or infectious diseases specialists' have written declining share from 74% to 38% during the same period. General practitioners provided a greater proportion (47%) of care in regional/remote areas than major cities.

Conclusions: Broad treatment access led to rapid initial increases in treatment uptake, but this uptake has not been sustained. Our results suggest achieving global elimination targets requires more than treatment availability: people with HCV need easy access to testing and linkage to care in community settings employing a diverse prescriber base.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects approximately 71 million people globally,[1] and an estimated 400,000 people die each year from hepatitis C-related liver diseases.[2] The new era of direct-acting antiviral (DAA) treatment has revolutionised hepatitis C care, with cure rates over 90% and short, well tolerated courses of tablets, providing a once in a generation opportunity to eliminate hepatitis C as a global public health threat. Recent World Health Organization targets aim to reduce new hepatitis C infections by 80%, and reduce deaths due to hepatitis C by 65% by 2030. However, success in elimination is contingent upon increasing testing, diagnosis, linkage to care, and low cost treatment enabling high-levels of treatment uptake and cure. Curing large numbers of people with hepatitis C infection reduces hepatitis C prevalence; in particular, curing individuals still engaged in transmission risk practices delivers an additive treatment-as-prevention impact by reducing the pool of hepatitis C infection within key populations, reducing disease incidence.

In Australia approximately 230,000 people were estimated to live with chronic hepatitis C in 2015, and costs of the hepatitis C burden without treatment was estimated at over AU$2.43 billion,[3] with the majority of infection occurring in people with current or past injecting drug use.[4] In 2015, there were 10,000 newly diagnosed cases of hepatitis C in Australia, [5] with prevalence among people who inject drugs (PWID) around 50% and an estimated annual hepatitis C incidence of around 7-8/100 person years among Australian PWID.[5-7]

Modelling suggests that elimination targets will be achieved fastest by rapidly scaling up highly effective treatments that particularly target high-risk individuals.[3,8,9] In countries such as Australia where the epidemic is driven by injecting drug use, relatively small increases in the percentage of PWID treated annually (from 1% at 2015 levels to 12% after DAA access) is predicted to reduce hepatitis C incidence by over 80% in the next decade.[8-13] [11,12,25-28]. To meet global incidence targets, in Australia this translates into approximately 4,700 treatment courses that need to be delivered to high-risk individuals annually for the next decade.[13] In addition, modelling demonstrates that to meet global mortality targets most quickly, an additional 5,300 treatment courses per annum need to be delivered to those with advanced liver disease over the first five years.[13] Crucially, treatment scale up needs to be *sustained* and *inclusive* of PWID who have been traditionally harder to engage in care. This needs to be coupled with scale-up of prevention initiatives including needle and syringe programs (NSP) and opioid substitution therapy (OST). With cost-effectiveness models

showing that treating hepatitis C among PWID is only modestly more expensive than treating non-injectors,[14] the pathway to elimination through broad treatment access appears feasible.

March 2016 was a watershed moment in Australia: these new highly-effective treatments became available for all people living with hepatitis C under the Pharmaceutical Benefits Scheme (PBS) at a cost of approximately US$800 million over four years. The PBS subsidises the cost of medicines after they have been licenced for use in Australia. To receive government subsidy, a new medication must undergo expert review for clinical and cost effectiveness. The cost of most medicines to all Australian citizens and permanent residents is capped at US$30 per month of treatment, or US$5 per month for people receiving low income welfare benefits. The final price paid by government for a medication often remains confidential. Due to the high price of hepatitis C medications initially, the cost to the Australian government for hepatitis C treatment was capped at approximately US$200 million annually under a confidential cost sharing arrangement; any excess cost due to large volume of prescriptions is borne by drug manufacturers. In addition, Australia has universal access to treatments, meaning there are no restrictions on who has access to treatment nor the numbers of times an individual can be treated. National guidelines recommend treatment for everyone living with hepatitis C infection, including PWID and prisoners.[15] Given the price of DAAs and universal nature of the PBS, government data systems capture virtually all hepatitis C prescriptions.

With a largely universal, publicly funded, health care and insurance system, the effect of these policy changes is that Australia has some of the key ingredients needed to eliminate hepatitis C as a public health threat over the next decade.[16] Australia is one of a few countries globally on target in this quest.[17] This elimination strategy will not be successful unless we treat large numbers of people at ongoing risk of hepatitis C transmission, including PWID, prisoners and HIV-coinfected gay and bisexual men.

Using the early experience of a country such as Australia, with a unified approach to treatment as a case study, factors facilitating and impeding high rates of treatment uptake are already evident. We aim to describe facilitators to hepatitis C treatment uptake after one year of universal access to DAAs across Australia, and potential barriers to sustaining up treatment uptake in future.

METHODS

We analysed PBS data to determine the number of prescriptions initiated from January 2013 to July 2017, which includes the first year of unrestricted DAA access (March 2016 – March 2017) as well as previous interferon-based treatment uptake. Based on the first dispensed prescription of each treatment course, we extracted data on number of prescriptions over time, treatment regimen, geographic location and provider type (general practitioner, gastroenterology/infectious diseases specialist, addiction/sexual health specilaists and other medical practitioner prescribers).

Treatment commencement was defined as the first medication dispensing date. Date of treatment commencement is recorded as when the PBS record the prescription being dispensed which may be delayed by days or weeks. We obtained commencement by three-month (quarterly) periods. Treatment regimen was categorised by peglyated-interferon-based or any available interferon-free DAA agent, which includes sofosbuvir, daclatasvir, sofosbuvir/ledipasvir fixed dose, grazeprevir/elbasvir fixed dose, or ombitasvir/paritaprevir/dasabuvir/ritonavir fixed dose, with or without ribavirin.

PBS aggregates data when five or fewer individuals have the same prescription, provider and location to protect against potentially identifying participants based on their treatment characteristics. To calculate number of treatment courses, any field with under six (but not zero) individuals was assumed to represent three individuals, leading to an average estimated error of one percent and maximum of three percent error in total treatment numbers. Geographic location was coded according to Statistical Area 3 (SA3), a geographical unit defined by the Australian Bureau of Statistics.[18] Australia has 338 SA3s, which each have a population of approximately 30,000 to 130,000 people. Remoteness Area classifications (major city, inner regional, outer regional, remote, very remote) are defined in Australia for smaller geographical units than SA3s, and population-weighted averages from each of the smaller geographical areas were used to create a remoteness area classification for each of the SA3s, and hence for where treatments were initiated.

RESULTS

Since subsidized DAA access in March 2016 until June 2017, 43,382 courses of therapy have been commenced; 32,877 courses commenced in 2016 (10 months of access), and 39,062 courses were commenced in the first four full quarters (after 13 months of access) (Table 1 and Supplementary Figure 1). Prescriptions peaked in the first three months after PBS listing at 13,109 treatment courses per quarter; treatment commencement has declined each

subsequent quarter to 5,320 prescriptions (63% decline since the peak commencement) up to end of June 2017. In the pegylated-interferon-based era (prior to April 2013) and first generation DAA era (2013-2015) a maximum of 2,185 individuals commenced treatment per quarter (in 2013Q3).

Following registration of interferon-free DAAs but prior to government subsidy, treatment initiation dropped substantially (Figure 1). There was a nadir of 361 individuals commencing treatment in the final quarter of 2015.

Prior to interferon-free DAA treatment, viral hepatitis specialists provided nearly all treatment as required by funding rules at the time; general practitioners were required to complete additional training to initiate interferon prior to 2016. Since interferon-free DAA treatment, hepatologists and infectious diseases physicians have accounted for the bulk of prescriptions (54%, Table 1). In the first quarter of DAA access (2016 Q2), 63% of prescriptions were prescribed by hepatologist/infectious disease specialists; 16% by sexual health or addiction medicine specialists, 16% by general practitioners, and remaining 5% by other medical practitioners (Table 1). Since then, the proportion of prescriptions written by hepatologists/infectious diseases specialists has declined (to 38% in 2017 Q2) while share of prescription written by general practitioners' had increased (to 37% 2017 Q2). Nevertheless, despite a shift in the share of prescriptions by practitioner type, the number of general practitioner prescriptions has remaining static over time; all other prescribers have written fewer prescriptions per quarter (Figure 2).

Most individuals received interferon-free DAA treatment from prescribers in major cities (78%) or inner regional areas (16%), which includes outer urban areas adjacent to cities. This corresponds to where 92% of the Australian population reside. Treatment was commenced in outer regional areas and remote areas for 6%, where 7% of the population reside. Fewer than 0.5% of all initiations were identified in very remote geographic areas which have limited prescriber and pharmacy services (Figure 3). An increasing proportion of prescriptions are commenced outside of major cities and regions over time, from 19% in 2016 Q1, to 26% in 2017 Q2. General practitioners provided an increasing share of hepatitis C treatment outside major cities: 50% of regional and 86% of remote prescriptions were GP initiated in 2017 Q2, although absolute treatment numbers prescribed by general practitioners remained stable over time.

Interferon-free DAA treatment commencements by state was approximately in proportion to population distribution: 33% in New South Wales, 27% in Victoria, 20% in Queensland, 6% in South Australia, 8% in Western Australia, 2% in Tasmania, 1% in Northern Territory, 2% in Australian Capital Territory.

DISCUSSION

Access to interferon-free DAAs dramatically increased the number of people undergoing treatment in Australia. However, despite Australia's health system supporting broad access at a relatively low cost to individual patients, and high diagnosis rates prior to the introduction of DAAs,[19] Australia has not sustained high treatment uptake. If Australia and other countries globally are to achieve the WHO elimination goals, the reasons for this fall in treatment uptake need to be better understood. Our work suggests key factors to be considered include engaging and linking individuals living with hepatitis C in care, and workforce education, distribution and capacity.

There are other well publicized examples of countries striving toward hepatitis C elimination through treatment scale up. After two years of treatment access in Iceland, 80-85% of the population of around 1000 people living with hepatitis C have been cured.[20] In the country of Georgia, approximately 34,000 people have started treatment after two years out of 46,000 diagnosed and 150,000 people living with hepatitis C.[21] These country-level programs emphasize the need for high rates of diagnosis, linkage to care *and* treatment uptake in order to achieve global elimination targets.

Maintaining high levels of hepatitis C treatment requires high levels of hepatitis C testing to ensure sufficient new cases are detected and linked to care. The WHO 2030 elimination targets call for 90% of hepatitis C-infected people to be diagnosed.[22] Currently many people infected with hepatitis C do not know they have the virus, and even amongst those who are diagnosed many are not linked to care. Many groups have demonstrated attrition along the testing stages of the care cascade globally.[23-26] Even in Australia, where 70-85% of people with hepatitis C infection are estimated to have been tested for hepatitis C antibodies in the past, there is a substantial decline in the HCV RNA testing to confirm chronic infection (estimated at 45-50% of those living with chronic HCV).[5,27] National modelling shows that to meet the elimination targets, there will need to be a substantial increase in hepatitis testing (both antibody and RNA) to feed into treatment uptake.[28,29]

Simplifying the care cascade and reducing the numbers of appointments patients have to attend to initiate treatment could greatly reduce loss to follow up and increase the numbers of people achieving cure.[30] In order to improve the care cascade locally, national strategies are now focusing on frequent, repeated HCV RNA testing (at least annually) in key risk populations as a mechanism to re-engage and link people to care. Point of care HCV diagnostic tests – which have been licensed for use overseas but are awaiting approval in Australia – will also play an important role in offering accessible, regular testing for populations at higher risk of infection. They have been piloted in Australian drug and alcohol settings, emergency departments, community health service, and prisons.[16,28] Since testing uptake is not captured in prescribing datasets, but may be recorded in other health service databases, future data linkage research to overlay testing and prescribing trends would greatly help understand gaps in our care cascade caused by insufficient testing.

Allowing general practitioners to prescribe DAA to maintain ongoing treatment uptake is essential. The data presented in this study demonstrate that GP prescribing has increased from the pre-DAA era but stabilising at around 1900 treatments per quarter over the last 12 months. The initial high uptake in treatment, with the high proportion of scripts written by specialists likely reflects the large pool of patients waiting for treatment in tertiary settings following a period of lower than average treatment from 2013-2015. The issue now is the rapid decline in treatment after the initial surge. GP prescribing appears to be particularly important outside of metropolitan where they are providing nearly half of all care. If GPs maintain current treatment numbers, combined with treatment in other sectors then Australia's elimination response will remain on target.[31] However if GP prescribing was to fall after a year or two (as occurred with the specialists) Australia may struggle to reach its elimination goals. There are over 27,000 GPs practicing in Australia, compared with fewer than 700 hepatologists.[32] Given that fewer than 10,500 general practice issued DAA prescriptions (Table 1), most GPs must have no experience prescribing hepatitis C DAAs. Further research is needed to understand why and examine how to support GPs to increase their prescribing numbers.

In Australia, as with most high-income countries, the group most affected by HCV are PWID,[33] yet this population remains the least-diagnosed, lowest-engaged and least-treated.[34,35] Rapidly and substantially increasing the numbers of PWID treated, engaged and retained in care is critical to reducing HCV transmission and burden.[8] A further advantage of

supporting non-hepatitis specialists to commence treatment is that they often service opiate substitution therapy, mental health and sexual health services where PWID are disproportionately engaged in care. Currently Australia's overall treatment numbers do not reveal whether sufficient PWID are receiving treatment to more rapidly reduce transmission; it has been estimated that 5000 PWID need to commence treatment each year to meet elimination goals.[13] Previous models of HCV epidemics where transmission is predominantly due to unsafe injecting drug use suggest that treating currently-injecting PWID will lead to significant reductions in HCV incidence and liver-related morbidity.[13,36,37] However these models clearly show that even with unlimited and unrestricted access to HCV treatment, as is the case in Australia, additional interventions to target PWID and enhance their access to HCV diagnostic testing, pre-treatment assessment, and retention in care are required to achieve elimination targets.[8]

The Eliminate C Partnership is a system wide response to the challenge in linking PWID to care. It is an Australian project involving government, researchers, health services and civil society to support new models of care. Its key purpose is to increase treatment access for key populations through health promotion and community engagement programs, systems change for rapid testing and re-testing, and providing nursing and peer support to clinics with high caseloads of key affected populations. Community-based care, pharmacist-led care and nurse-led treatment are all being developed as methods of increasing testing and linkage to care.[38] They have informed revisions to guidelines in Australia, where community care models for PWID are now considered routine.[15] Prescriber awareness of testing and linkage to care is being supported through the Eliminate C Partnership, national education programs provided by professional societies and community organisations, and state based education and training consortia funded by government. Interventions to increase testing in general practice including incentives, peer support, clinical audit tools, and active case finding of those previously tested are being tested at a local service level.

National prescribing data in Australia has limitations. First, there is some delay in reporting prescription data, meaning some treatment commencements might have occurred up to a few weeks prior to reporting, and hence underestimate the most recent quarters' data. However, these reporting delays are likely to remain similar over time and therefore are unlikely to have affected the trends reported here. Secondly, given privacy considerations, individual patient level data is not released in the entire dataset. Granular data on exact prescription by provider and geographic area, including patient demographics, is collected but censored

before release. This limits any analysis based on individual predictors of treatment commencement, including the ability to accurately determine the number of people with cirrhosis, comorbidities, drug use, PWID, prisoners or HIV-coinfection receiving treatment.[39] Thirdly, prescribing data is not linked to clinical outcome data in Australia at present. This represents a missed opportunity to definitively and directly report real world cure rates and any changes in epidemiology brought about by treatment. Moves are underway to address this gap in monitoring through enhanced surveillance systems and linked cohorts; nevertheless, prescription data collected by the national government is likely to remain outside that surveillance system. Finally, the data count all treatment initiations as separate individual cases and cannot count retreatment as yet. Modelling from the USA projects the need for retreatment in around 8% of all individuals each year.[40] This might falsely inflate the estimates of individuals treated, but given the data is largely from year one, after allowing for treatment and follow up time, the number of people being re-treated with DAAs is probably very small to date. Notwithstanding these inherent limitations, this analysis allows for the formation of hypothesis around service gaps, and importantly, provides context and justification for future well-designed cohorts or interventional studies to better understand and enhance treatment access.

In conclusion, rapid treatment uptake over the first year in Australia was very high, although perhaps not unexpectedly, was not sustained. The challenge for Australia, and other similar countries, is to ensure that following the initial enthusiasm for treatment, that treatment numbers are sustained at a level sufficient to achieve elimination. Key factors in ensuring this occurs includes removing all unnecessary barriers to testing and care, and allowing and encouraging general practitioners to prescribe treatment. It is also critical that there are high levels of engagement and treatment amongst people in high risk groups where ongoing transmission is occurring. Experience suggests this will not happen by chance and a focussed effort is required to ensure treatment scale up for these groups to the levels identified in the elimination models. Our observations have international significance as other countries move towards unrestricted treatment access. Treatment subsidies are necessary but will be insufficient alone to reach the WHO elimination targets. Universal treatment needs to be combined with enhanced prevention, testing, linkage to care, and treatment programs that are easily accessible to all people with chronic hepatitis C infection.

DECLARATION OF INTERESTS

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ABBREVIATIONS

HCV, Hepatitis C virus; DAA, direct acting antiviral therapy; PEG-IFN, pegylated-interferon; RBV, ribavirin; PWID, people who inject drugs

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TABLES

Table 1: Hepatitis C direct-acting antiviral treatment commencement in Australia per quarter by provider type (% of all prescriptions)

	General practitioner	Hepatology/ Infectious Disease specialist	Addiction/ Sexual health specialist	Other medical practitioners	Total per quarter
2016 Q1	387 (9%)	3021 (74%)	510 (12%)	192 (5%)	4110
2016 Q2	2114 (16%)	8248 (63%)	2110 (16%)	637 (5%)	13109
2016 Q3	2173 (24%)	4931 (54%)	1673 (18%)	365 (4%)	9142
2016 Q4	1861 (29%)	3119 (48%)	1260 (19%)	276 (4%)	6516
2017 Q1	1979 (32%)	2703 (44%)	1250 (20%)	253 (4%)	6185

2017 Q2	1964 (37%)	2037 (38%)	1116 (21%)	203 (4%)	5320
Total by prescriber	10478 (24%)	24059 (54%)	7919 (18%)	1926 (4%)	44382

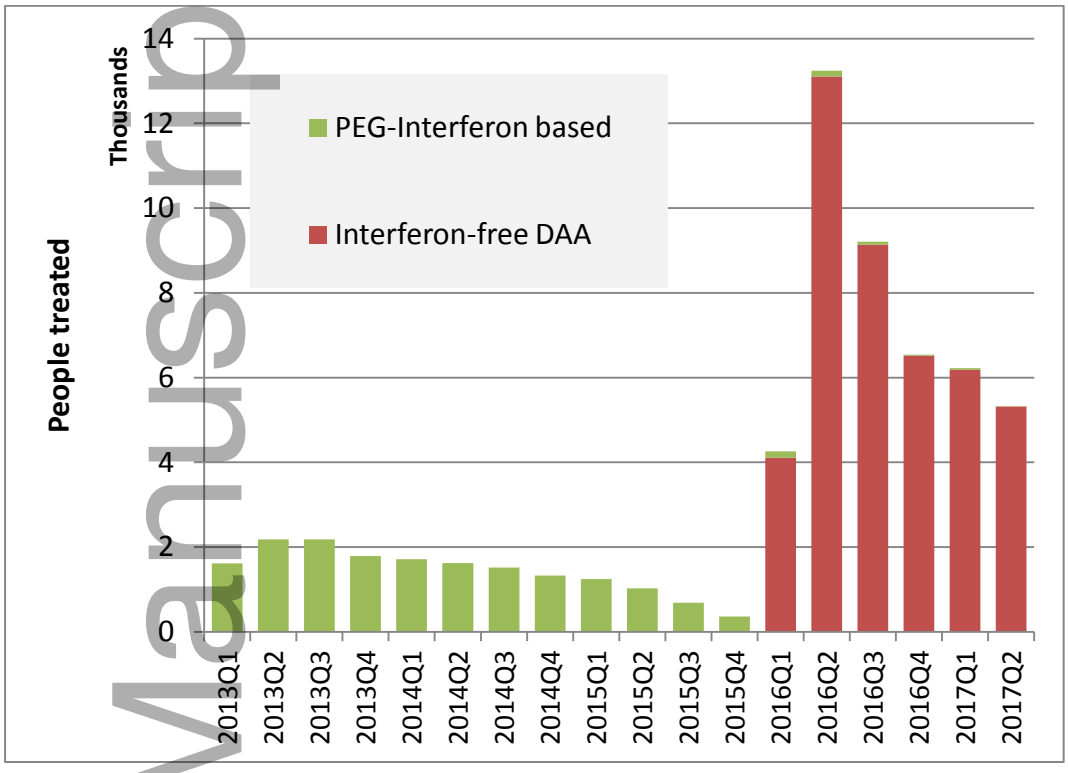


Figure 1: Hepatitis C treatment commencement per quarter in Australia by treatment regimen (interferon based versus direct-acting antiviral) from 2013-2017

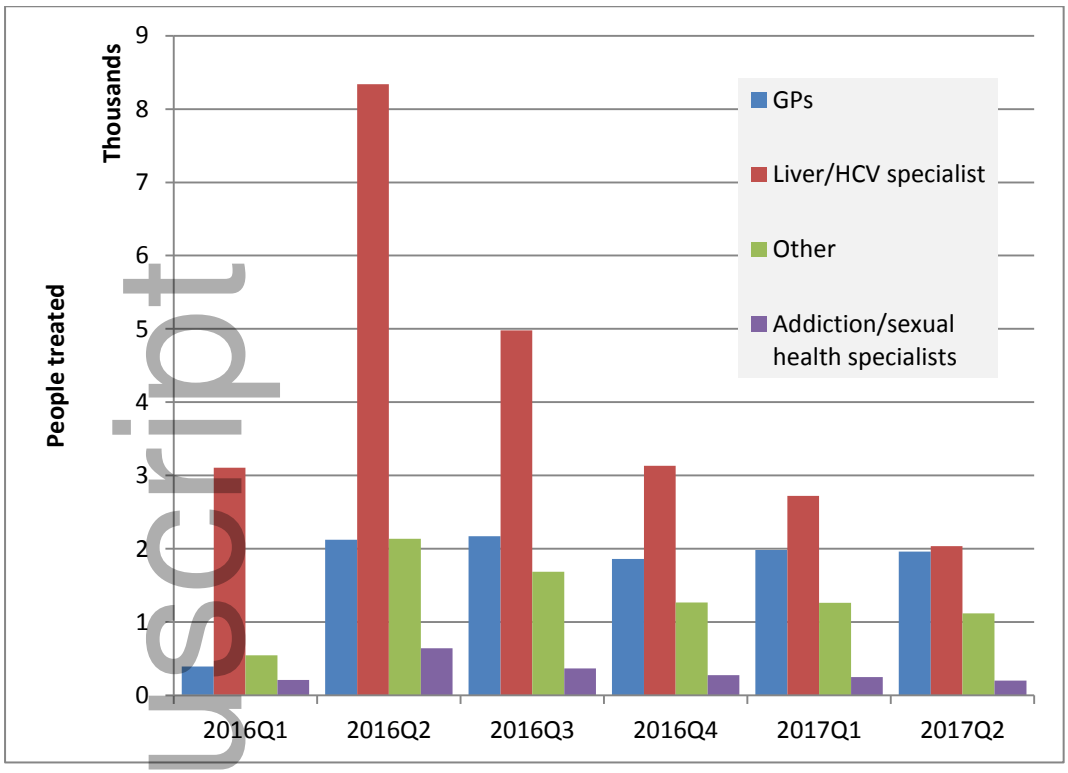


Figure 2: Hepatitis C direct-acting antiviral treatment commencement in Australia by prescriber over time since universal access from 2016

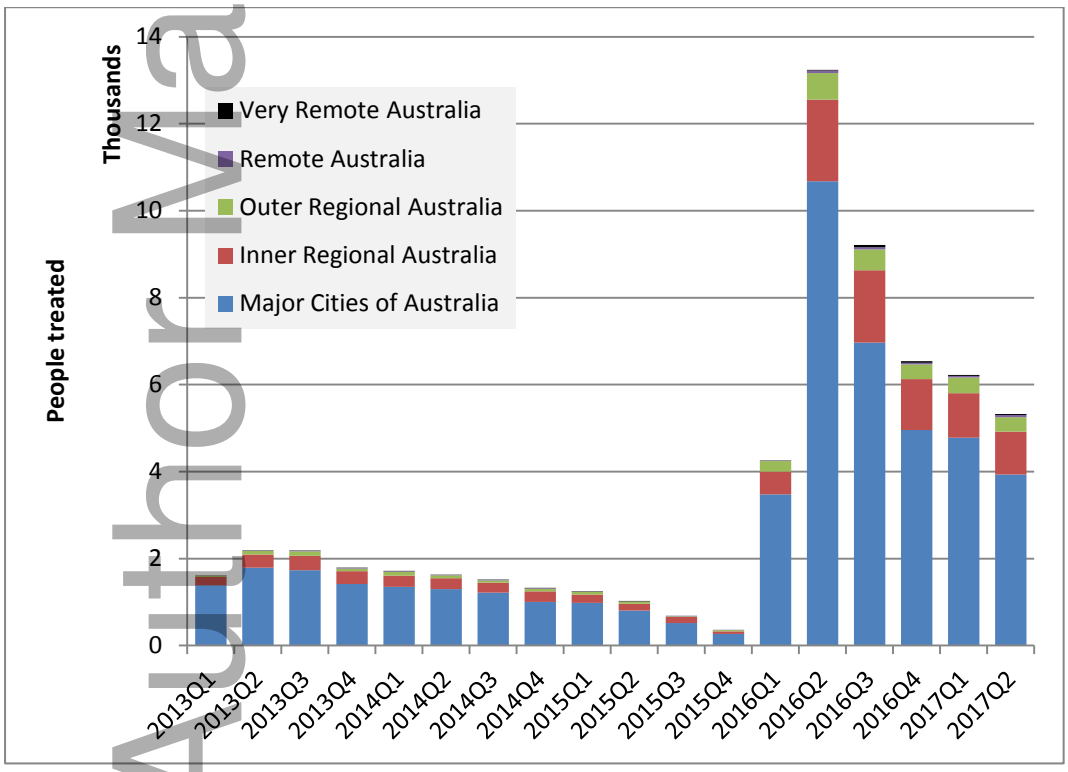
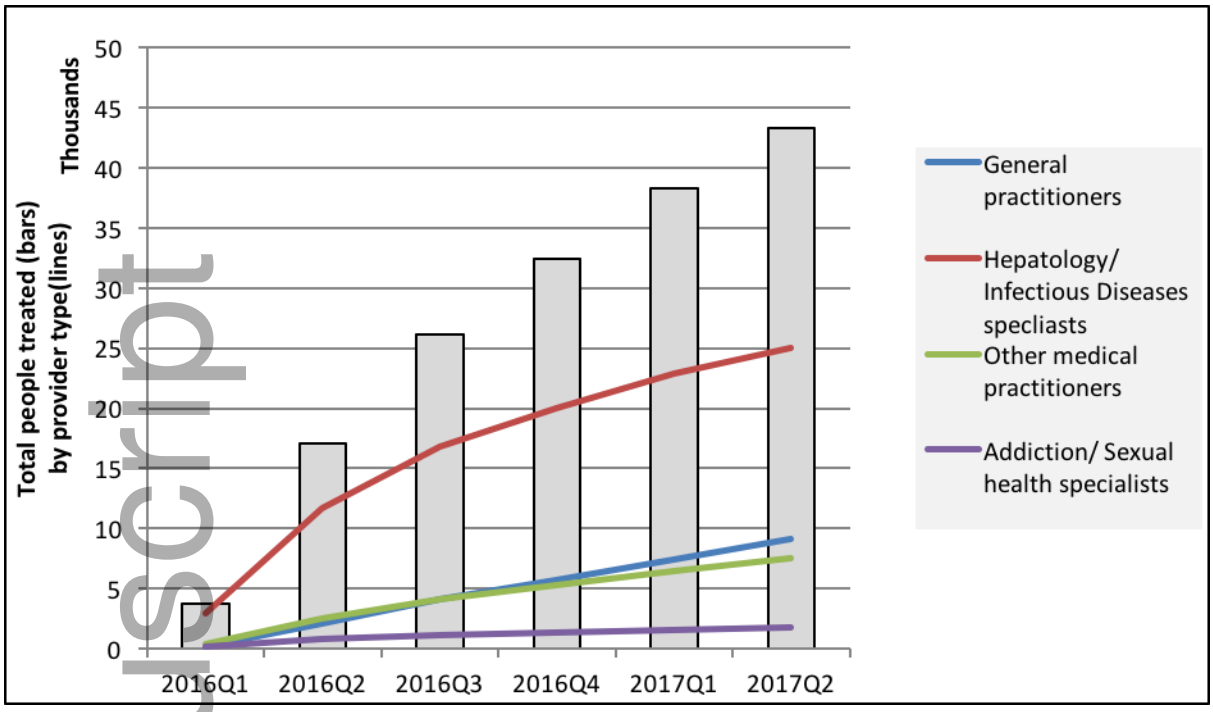


Figure 3: Hepatitis C direct-acting antiviral treatment commencement in Australia by geographic area over time 2016-2017



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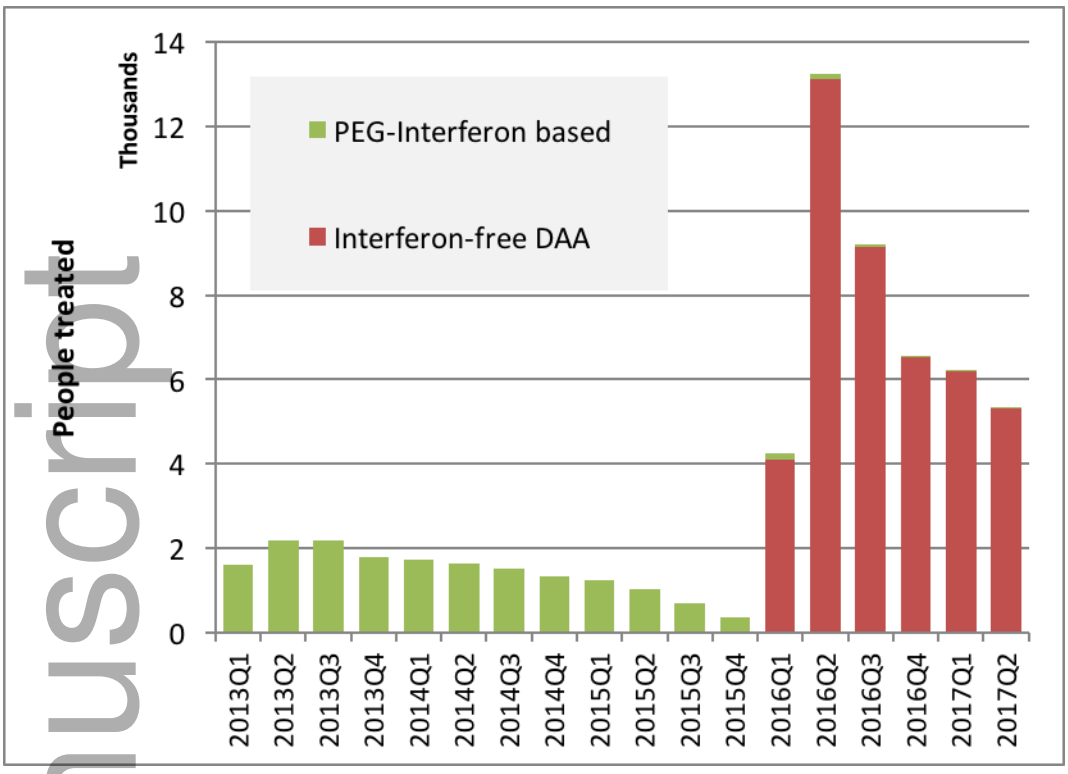

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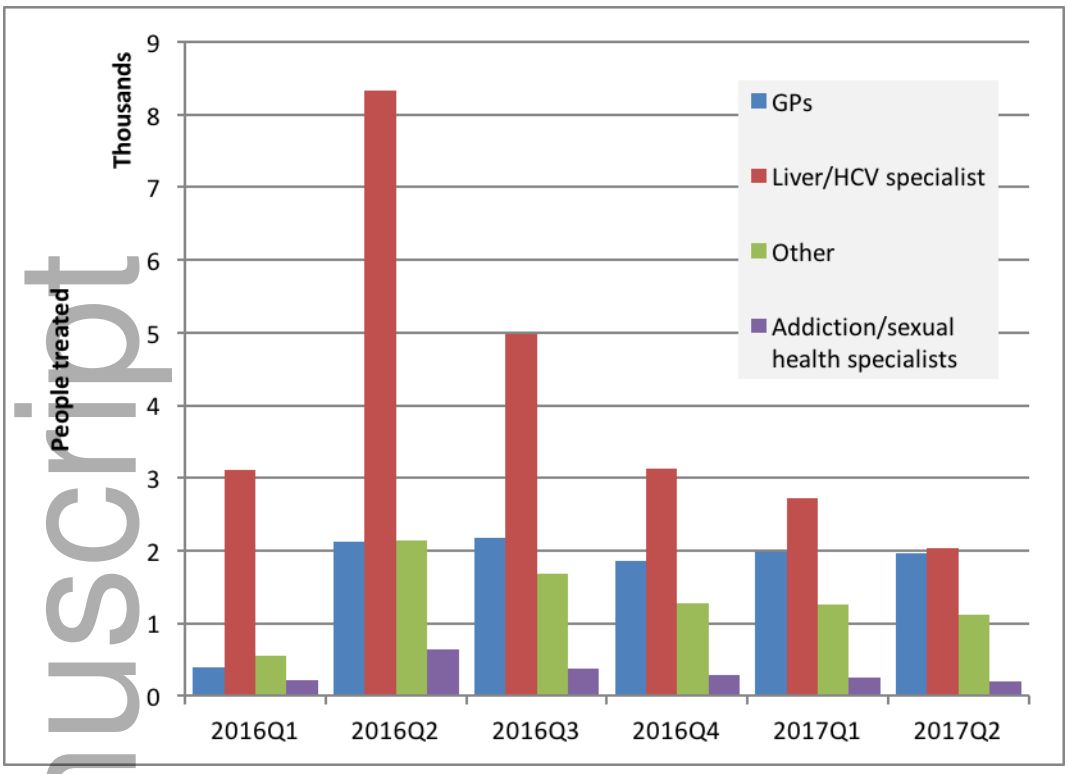
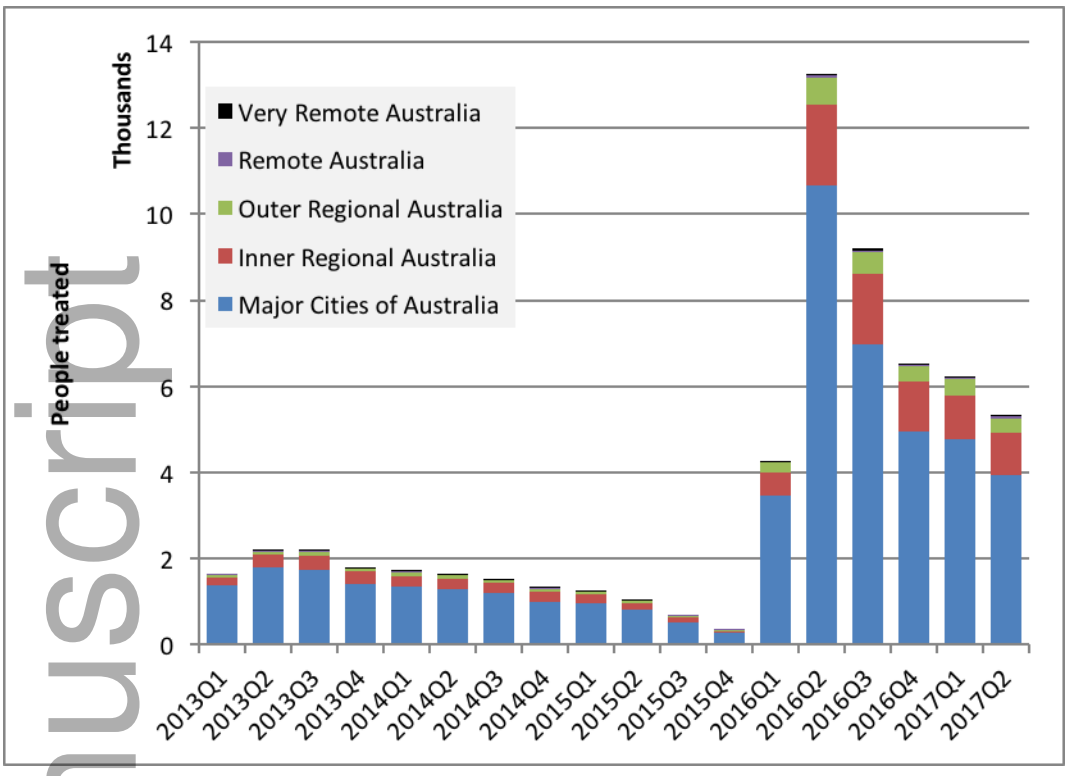


apt_15210_f3.png



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