Reducing liver disease-related deaths in the Asia-Pacific: the important role of decentralised and non-specialist led hepatitis C treatment for cirrhotic patients

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Finding new ways to increase access to hepatitis C (HCV) treatment is integral to reducing liver disease-related deaths and achieving HCV elimination in the Asia-Pacific. Decentralised, non-specialist led care is essential to expand access to HCV treatment, both by increasing the number of providers and the geographical coverage. The vast majority of direct-acting antiviral (DAA) treatments for HCV do not need to be provided by a specialist. While all patients should have appropriate liver disease assessment prior to treatment to determine the degree of liver fibrosis or cirrhosis and the severity of liver function impairment, most patients - including those with compensated cirrhosis - can be treated with DAAs by non-specialist practitioners (e.g. general practitioners (GPs)) in primary care settings.1 GPs treating HCV patients with compensated cirrhosis will be critical to ensuring adequate access to specialists for those who require specialist care for decompensated cirrhosis.

For the first time there has been a reduction in HCV-related deaths globally, clearly demonstrating the impact and benefits of striving for HCV elimination. Despite this, treatment coverage remains low in the Asia-Pacific region, ranging from 5% in South East Asia to 10% in the Western Pacific.2 Only four countries in the Asia-Pacific (Australia, Japan, Mongolia, and Georgia) are on track to reach the World Health Organisation (WHO) elimination goals by 2030.3 Approaches adopted by these countries may be valuable for other countries pursuing elimination goals; common to all four is strong political commitment to achieving national targets through low-cost or subsidised testing and treatment programs.5,6 For example, Mongolia undertook epidemiological work to inform the national targets, pursued options for generic DAAs, included these low cost DAAs into the national health insurance scheme, launched a nation-wide screening program, and delivered HCV treatment through integrated services within the primary healthcare system.4,6,7
More than half of the countries within the Asia-Pacific region are classified as low- or middle-income countries (LMICs). Many LMICs face multi-faceted barriers to scaling up access to HCV care: low public awareness of HCV, inadequate specialist workforce, limited implementation of decentralised care within existing health systems, and the unaffordable price of diagnostics and DAAs. In most LMICs, there are not enough specialists to provide care to those requiring their services. Furthermore, the specialist workforce is often concentrated in major urban health centres. In the case of HCV, the high workloads of specialists lead to long waiting times for patients, hampering timely treatment and leading to many becoming disengaged from care. While the cost of diagnostics and DAAs remains a barrier to scaling up access to HCV care, the price of DAAs is continually declining, and some promising patent-free options are in the pipeline. However, achieving global HCV elimination requires more than mere access to affordable DAAs.

Increasing access to treatment is integral to reducing liver disease-related deaths and achieving HCV elimination. One way to achieve this is to train non-specialist practitioners (e.g., GPs, nurse practitioners, pharmacists) to treat HCV with DAAs. We call for a renewed focus on treating people with compensated cirrhosis in primary care. This will allow for increased access to treatment for all and give priority access to specialists for those who require specialist management. General practitioners and other non-specialist providers in primary care settings can easily treat HCV in those with compensated cirrhosis, without the need of a specialist. Referral to the specialist for further evaluation of ongoing liver disease can be done after the completion of DAA treatment. This approach will ensure that people with HCV cirrhosis are treated early, preserving liver function and reducing the risk of liver cancer. Evidence from a study using transient elastography to measure liver stiffness found that approximately one third of cirrhotic patients were reclassified as non-cirrhotic post-SVR. Another study found that those with Child-Pugh A cirrhosis had significantly reduced likelihood of clinical disease progression if they achieved SVR, compared to those who did not achieve a cure. Evidence from these studies demonstrate how treatment induced cure reduces the risk of liver disease progression and the risk of developing liver cancer.

In addition, reducing the number of patients referred to specialists for DAA treatment will allow specialists more time to provide appropriate treatment to patients with advanced liver disease. Even in LMICs, strategies to reduce progression of cirrhosis among those with decompensated cirrhosis are available, for example: use of beta-blockers to reduce portal hypertension, banding of oesophageal varices in bleeders and those at high risk of bleeding (requiring access to endoscopy), and the use of lactulose to prevent hepatic encephalopathy.

Key to expanding safe and effective HCV treatment by GPs is the development of clear HCV testing and treatment guidelines, and the simplified tools to assess the degree of fibrosis or cirrhosis and whether the cirrhosis is compensated or decompensated, prior to initiating treatment. Identifying whether a patient has decompensated cirrhosis and requires referral is a pillar of differentiated care, where specific groups receive different levels of care depending on need. Liver disease assessment can be performed by trained non-specialist practitioners in primary care settings. Transient elastography of the liver (e.g., FibroScan®) is currently used as best practice, as it provides a clear clinical picture of the liver fibrosis and aids with planning post-DAA therapy care. However, FibroScan® technology has accessibility and affordability issues for many people in the Asia-Pacific. Further, FibroScan® is a specialised technology for liver fibrosis assessment which requires frequent maintenance, and intensive training for operators to perform the scan and interpret the results. Recognising this, the WHO Guidelines for HCV treatment (2018) recommend aspartate aminotransferase (AST)/platelet ratio index (APRI) score or FIB-4 test to assess liver fibrosis in resource limited settings. Many settings, APRI score is used to triage patients for FibroScan®. In others, it is used in conjunction with assessment for physical signs of liver decompensation. For example, the Myanmar National Guidelines require GPs to calculate the APRI score to decide treatment duration and to refer those with physical signs of hepatic decompensation to a specialist. The Pakistan HCV Testing and Treatment Guidelines also allow GPs to decide the duration of treatment based on APRI score, and only refer those with APRI >1.5 to a specialist. The simple blood tests (AST, platelets) required for APRI score are widely available in most settings. Furthermore, it is worth noting that the presence of compensated cirrhosis does not change treatment duration recommendations for some treatment regimens. DAAs are safe and effective in people with compensated cirrhosis, and HCV eradication through DAA therapy is itself associated with reduced risk of developing cirrhosis and liver cancer. As such, HCV treatment should not be unduly delayed by requirements for special tests for cirrhosis (e.g. FibroScan® ultrasound); especially in settings where the specialist management for portal hypertension or liver cancer screening is not widely available or utilised.

Task-shifting to GPs and decentralisation of care into primary care settings is supported by growing evidence globally. Systematic reviews have shown GPs can safely and effectively perform liver disease assessment...
and initiate DAA therapy for compensated cirrhotic patients in community settings, resulting in few adverse outcomes and high sustained virological response (SVR12) rates.\textsuperscript{7,25} Ensuring patient safety is paramount, and this can be facilitated through use of quality-assured diagnostics and laboratories, and through adequate training and support for GPs. Clear clinical decision-making tools, including APRI score calculator, drug-drug interaction checkers, and summary tables of key pre-treatment assessments and treatment options, are available in many settings to support GPs to prescribe DAs. For example, the EC toolkit in Australia was developed to collate available tools and develop extra tools to address unmet needs within primary care in Australia (see: https://ecpartnership.org.au/toolkit).

Task-shifting care to GPs and decentralisation into primary care settings will allow for increased access to HCV treatment outside of urban centres, ensuring more equitable access to care. Country-specific assessments on where to focus efforts, considering the epidemiology of disease burden, will be required to inform distribution of resources needed to serve the general population, or various key population groups including people who inject drugs, people in prison, or people living with HIV. Implementation of robust national data systems would improve the data available to inform strategies and to monitor progress. Such country-specific assessments can also help inform the testing strategy and assist practitioners to target testing, either through regular testing of key population groups and/or to general population one-time screening: the approach will be country-specific based on estimated HCV prevalence among general population and key population groups, considering resource availability.\textsuperscript{24} With low-cost rapid diagnostics available for screening, it is unlikely that excessive screening of HCV will occur; however, it is important to ensure all those who screen positive have access to confirmatory nucleic acid testing to diagnose active infection.

Successful implementation of simplified clinical pathways in secondary and tertiary based hospitals, and some at decentralised HIV treatment sites, through national programs has been demonstrated in Myanmar, Cambodia, India, and Indonesia.\textsuperscript{5,7} Our work in Myanmar and recent work from Cambodia showcase feasible and effective models of care for community-based treatment, using simplified clinical pathways.\textsuperscript{16,17} Both studies found that treatment of compensated cirrhotic patients by GPs at community-based sites was safe and effective, with high cure rates and few adverse events. Uptake of treatment was high and there was limited loss to follow up from care.\textsuperscript{15,17} Task-shifting to GPs required minimal training. Setting clear referral criteria and pathways was important in the Myanmar model for ensuring GP confidence.\textsuperscript{15} Decentralised and non-specialist led care has been successfully implemented in many countries in the Asia-Pacific region. In the Western Pacific region, a recent review of progress towards HCV elimination found that ten countries have now expanded their hepatitis services into primary care.\textsuperscript{7} For example, in Malaysia following pilot of decentralised care in primary health care clinics, now 146 primary healthcare clinics are providing treatment, with care mostly provided by trained GPs.\textsuperscript{29} In Australia, GP-led HCV treatment is common; almost half of patients initiated onto treatment from 2016 to 2020 had their prescription written by a GP.\textsuperscript{29} Initially, remote specialist consultation and approval was required by GPs without experience prescribing DAs. This was facilitated through remote consultation forms and successful allowed treatment of cirrhotic patients by GPs where access to a specialist was limited.\textsuperscript{10,31} A similar process also occurs for the nurse-led prison treatment service in Victoria, Australia where nurses could provide treatment to those in prison via remote consultation form for those without cirrhosis or with compensated cirrhosis.\textsuperscript{14} Simplified care models with non-specialist practitioners prescribing DAs could be scaled to reach the level of coverage we need to achieve elimination goals, especially in LMICs where there are very few specialists.

Our challenge now is to ensure that national guidelines allow GPs and other non-specialist practitioners to treat patients with compensated cirrhosis, to provide frequent training for these practitioners, and to develop clear, effective referral pathways for specialist review or advice. Training, mentorship, and support to GPs can be provided remotely through the Project ECHO (Extension for Community Healthcare Outcomes) model.\textsuperscript{13} Project ECHO is a tele-mentoring hub-and-spoke model where one hospital provides multi-disciplinary support for a network of primary care providers through use of frequent meetings for specialists to share best practices on HCV testing and treatment, and for community providers to share de-identified case presentations for discussion and recommendations for a treatment plan.\textsuperscript{13} Evidence from hepatitis C and other diseases / specialty areas has shown that a Project ECHO tele-mentoring model can be used successfully for training, ongoing support, and provision of continuous medical education.\textsuperscript{31,32} Another option for specialist support is through the use of remote consultation with a specialist; described in detail above, this process is widely used by GPs in Australia.\textsuperscript{10,31}

Other considerations for successfully embedding HCV care into primary care include: encouraging GPs to get trained and provide HCV care, accessibility of laboratories for HCV RNA testing and liver function tests, and navigating the competing workloads of GPs in primary care; these must be addressed within each local context. While ideally all cirrhotic patients treated by GPs will then receive ongoing post-DAA therapy liver care to monitor for liver disease progression, in particular liver cancer surveillance through biannual ultrasounds, this is
unlikely to be feasible or widely accessible in most resource-constrained settings and alternative more-pragmatic clinical guidelines are also needed. For example, ultrasounds are available in private clinics and hospitals in Myanmar, but access is limited in the public health system; biannual ultrasound, alfa-feta-protein and platelets is recommended where possible, to ensure those who require specialist management can access it. By focusing on treating patients with cirrhosis early we can reduce the future burden of liver disease in resource-constrained settings across the Asia-Pacific region.

Decentralised care and non-specialist led HCV care will be key to expanding testing and treatment to all people affected by HCV. It is time to invest in scaling up decentralised care, along with training GPs, to ensure that all those living with HCV have access to a cure, particularly those with cirrhosis who are most likely to benefit from timely treatment to reduce their risk of liver disease progression.

Declaration of interests
MH has received investigator-initiated grant funding from Gilead Sciences and Abbvie for unrelated work. AP has received investigator-initiated grant funding from Gilead Sciences and Abbvie and honoraria from Gilead Sciences for unrelated work. AT has received consulting fees for advisory board participation and speaker fees from Gilead Sciences, Abbvie, Merck and BMS for unrelated work. AT also served on the board of directors for Gastroenterological Society of Australia (honorary position). WLY has received Gilead Sciences Public Health Award for unrelated work. KPK has received non-financial support from Mylan (support to attend AASLD Conference), Hetero for DAAs for Myanmar Liver Foundation Charity Clinic and Royal Ruby for donation liver supportive therapies for Myanmar Liver Foundation Charity Clinic. WN has received non-financial support from Mylan and Cipla to attend AASLD Conferences. JH has participated in Data Safety Monitoring Board for Gilead Sciences and has served on the Liver Faculty Australian Liver Association (Gastroenterological Society of Australia). All others declare no potential competing interests.

Role of the funding source
No specific funding source for this manuscript. The CT2 Study which informed this work was supported by Unitaid, through the FIND-led HEAD-Start project grant.

Author contributions
BD wrote the original draft, conducted literature search, and edited the manuscript to incorporate co-authors' inputs. JH conceptualised the idea, and reviewed and edited multiple drafts. WLY, AP, KPK, HH, WH, WN, AT and MH provided input on evidence to include, reviewed and edited draft manuscripts. AP, MH and JH provided supervision. All authors revised the paper critically for intellectual content and approved the final version.

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