The hepatitis C treatment revolution: how to avoid Asia missing out

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Abstract

The Asia-Pacific region bears a high burden of hepatitis C virus (HCV) infections and the largest number of global deaths. Populations most at risk of infection and disease progression include people who inject drugs and those living with HIV. HCV treatment options have rapidly expanded in the past few years through the development of direct-acting antiviral (DAA) medicines, which can cure HCV in over 95% of cases, but are prohibitively expensive. While price is the major barrier to treatment access, voluntary licensing has resulted in limited availability of one DAA (sofosbuvir) through generic manufacturers in India. Regulatory barriers, such as the need for domestic clinical trials, cause further delays in local medicines approvals and access. Intensive advocacy by civil society in combination with mobilisation of global resources for HIV treatment were critical to achieving price reductions in HIV medicines in the early 2000s. While the current global economic situation is less conducive to substantial funding support for HCV treatment, community advocates are building awareness of the growing opportunities for HCV cure. Key immediate steps include the inclusion of DAAs in domestic essential medicines lists, as the World Health Organization has already done for globally, and fast-tracking domestic drug approvals to facilitate government-level price negotiations with originator and generic pharmaceutical companies. Urgent action by a broad range of stakeholders is needed to facilitate access to HCV treatment in order to ensure that the millions of people living with hepatitis C in the Asia-Pacific will not miss out on these life-saving treatments.

Keywords: hepatitis C, Asia, Pacific, treatment, DAA

Introduction

Over the last 5 years, we have witnessed a relative explosion of new treatment options for hepatitis C (HCV) infection. We are now at the horizon of what could be a future without HCV. However, the initial prices for these treatments are up to US$100,000 per course, leading many to wonder if global treatment access and HCV eradication will be possible. Hepatitis C is an urgent health priority for the Asia-Pacific region, which bears the greatest global burden of hepatitis-related deaths.

It is estimated that up to 87 million people are currently living with HCV in the region, and that it is responsible for more than 50% of all HCV-related mortality worldwide – approximately 370,000 deaths each year [1,2]. HCV is primarily transmitted by blood-to-blood contact, such as through exposure to poorly screened blood products, non-sterile injections for medical care and the use of contaminated drug injecting equipment and related paraphernalia. HCV is less frequently transmitted by unprotected sexual intercourse [3], although sexual practices involving trauma to skin and soft tissues, and HIV co-infection, are conducive to HCV sexual transmission [4,5]. Vertical transmission of HCV does occur, although the general risk is low at around 3% [6,7]. The risk of mother-to-child transmission increases with maternal HIV coinfection to almost 20% [8].

Changing routes of transmission in Asia

Over the past half-century, HCV infection patterns have changed across the world, resulting in differing patterns of HCV transmission. Although iatrogenic transmission through contaminated blood products and medical injections was the major mode of transmission in the 20th century, increased use of sterile medical injections and screening of blood products has meant that their relative contributions to new HCV infections, including in many resource-limited settings, have fallen and those occurring through injecting drug use have increased. This is especially the case in middle-income countries like Vietnam and China.

In high-income countries, the vast majority of HCV transmission already occurs among people who inject drugs (PWID). In addition, high levels of HCV transmission within prisons occur in the region, especially in East and South East Asia, related to a variety of high-risk behaviours in these closed settings [9]. Evidence from other regions suggests rising HCV transmission among men who have sex with men (MSM), in particular among those already infected with HIV [10–12]. Few data are available to confirm this in the Asia-Pacific region.

Given common modes of transmission, the epidemiology of HCV/HIV co-infection follows similar patterns to HCV mono-infection [13], primarily impacting the key affected population of PWID. Most studies of HIV-positive PWID in Asia have shown that HCV is almost universal among them, and there are an estimated 735,000 and possibly up to 1.4 million HIV-positive PWID in the region [14,15].

Hepatitis C-related liver disease and the influence of HIV infection

Chronic liver inflammation because of HCV infection results in liver fibrosis, with progression correlating with the time since infection – age being a surrogate. Notwithstanding risk factors for progression, on average it is estimated that 20 years after exposure, 16% of individuals will have progressed to liver cirrhosis [16]. The 5-year risk of progression from compensated to decompensated cirrhosis is estimated at 18% [17]. Moreover, cirrhosis is a precursor for the development of hepatocellular carcinoma (HCC). The incidence of HCC in patients with cirrhosis is around 1–5%, although studies have found it as low as 0.5% and as high as 7% [18–20].

HCV/HIV co-infection complicates or hastens the progression of HCV-related liver disease. These individuals are less likely to
spontaneously clear HCV [21] and liver disease progression is accelerated [22]. As a result it has been estimated that approximately 21% of HCV/HIV co-infected individuals have cirrhosis by 20 years after infection and around 49% at 30 years [23]. Even with combination antiretroviral therapy (cART), mortality in co-infected individuals is up to 50% higher than in those with HIV alone [24]. Effective treatment interrupts disease progression and can provide clinical benefit and regression of liver damage, even in the presence of cirrhosis [25].

HCV treatment with direct-acting antivirals

Long labelled the silent epidemic, the emerging HCV treatment revolution has led to renewed interest in tackling this disease among advocacy and patient groups, and health policy makers. New, highly effective HCV direct-acting antivirals (DAAs) have now reached the market in a number of high-income countries. These oral drugs can be taken for shorter periods, have higher cure rates than previous treatments, and are effective across multiple HCV genotypes.

While there are multiple ongoing clinical trials testing over 50 compounds, there are now five DAA combination therapies that have been approved by regulatory authorities in at least one jurisdiction and recommended in international HCV treatment guidelines [26,27]. The World Health Organization is set to release its updated DAA HCV treatment guidelines later in 2015. New HCV DAAs are relatively simple to use compared to interferon-based regimens. Side-effect profiles are minimal and there is less need for repeated HCV-RNA tests, minimising the additional monitoring and care costs associated with these new therapies. At the clinical interface, this means treatment requirements can be considerably simplified, reducing training requirements and increasing the likelihood that non-specialist providers can provide treatment to larger numbers of patients.

However, HCV health and treatment literacy remains poor across the Asia-Pacific among patients and healthcare providers. Generating demand for HCV treatment in the region will entail having to build knowledge of the consequences of HCV infection among patients and communities, including knowledge of cirrhosis and liver cancer, and of the effectiveness of new treatments. Training of healthcare providers in screening, care and treatment for HCV will also be important, as will ensuring the quality of clinical practice in both the public and private sectors.

The challenges leading to poor access to DAAs in the Asia-Pacific

In the Asia-Pacific, new DAAs are almost exclusively available in selected high-income countries. There are two major barriers to achieving access to these medicines: price and regulatory approval. Prices for new DAAs are extremely high in high-income countries, and unaffordable for low- and middle-income countries. The only exceptions to this are Pakistan and Mongolia, which have recently negotiated substantial price reductions for selected DAAs. Both these countries have large HCV epidemics, a result of previous healthcare-associated transmission, and have significant political and public interest in addressing HCV through improved treatment access.

The pricing issue has many parallels with the global HIV response in the early 2000s. Lower prices for effective HIV medicines led to substantially increased access to combination antiretroviral therapy (cART). These prices were achieved through a combination of mechanisms including: (1) advocacy by affected communities; (2) pooled and joint procurement agreements or opportunities by large entities (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, GFATM); (3) increased demand for HIV medicines by the mobilisation of a co-ordinated international response; all underpinned by (4) an unprecedented expansion of generic manufacturing. Consequently, the price for cART has fallen from several thousand dollars per person per year to below US$100. Unfortunately, there is not yet a similar consolidated effort by the international community for HCV medicines procurement mechanisms that could reduce prices through a combination of negotiating pressure and market mechanisms. Indeed, currently there is no global platform or dialogue available through which this might be possible.

The second major barrier to DAA access is regulatory. While some countries, such as Mongolia, have fast-track mechanisms for the regulatory approval of new medicines, many others do not, which results in considerable delays in getting these drugs to the public market. In addition, some countries, including China and Vietnam, require domestic clinical trials for new medicines manufactured by foreign companies, despite stringent regulatory entities such as the US FDA or European Medicines Agency already granting approval. The registration and approval processes for new medicines can consequently require several years before access can be assured, and which further delays inclusion in national health insurance schemes. This is the case for DAAs currently in a number of jurisdictions in the Asia-Pacific region.

In the Western Pacific, the World Health Organization (WHO) is working with member states to draft a Regional Action Plan for Viral Hepatitis. While the overarching aim of the plan is to establish a normative public health approach to viral hepatitis across the region, addressing price and regulatory constraints at the supracountry level is also a key component. This Action Plan will be considered by the Regional Committee for the Western Pacific in October 2015, and could provide a common platform for advocating for access to DAAs in this region. One component of the Regional Action Plan is to support the development of comprehensive national hepatitis action plans in partnership with key stakeholders, including affected communities. These efforts should aim to institutionalise viral hepatitis control – individualised within Ministry of Health structures – to ensure the long-term viability of hepatitis prevention and management interventions, and to address country-specific issues such as stigma and discrimination. This would be in addition to regulatory issues, including early drug registration based on existing external regulatory agency approvals, collaborative regulatory processes such as WHO prequalification mechanisms, and intensive pharmacovigilance, especially for generic products.

Civil society mobilisation

The central role of community organisations and local and international NGOs in addressing these barriers cannot be overemphasised. Building on two decades of civil society engagement to address barriers to HIV treatment, several HIV-focused and related organisations have started to aggressively address critical barriers to HCV treatment access. In Eastern Europe, Asia, Africa and Latin America, civil society organisations have been mobilising to increase HCV awareness among most-affected communities, denounce exorbitant medicine prices and challenge patent regulations. This has been complemented by efforts to address the stigma and discrimination within society and medical institutions against those with HCV, lobby for resource mobilisation (both domestically and globally) to address hepatitis epidemics and begin implementing projects providing testing and effective treatment. Encouragingly, specific recent achievements have included the addition of key HCV medicines to the WHO List of Essential Medicines and the acceptance of HCV as a target disease (as an HIV comorbidity) in Global Fund or UNITAID-funded projects. Earlier community mobilisation efforts led to the naming of World Hepatitis Day and two UN World Health Assembly
resolutions on hepatitis (2010, WHA63.18; 2014, WHA67.6). The continued growth of community and patient groups in advocating for access to these scientific breakthroughs in hepatitis treatment were the backdrop to the inaugural World Hepatitis Summit in Glasgow in September 2015, co-organised by the World Hepatitis Alliance and the World Health Organization. The Glasgow Declaration for Hepatitis was a consensus statement from participants at the Summit calling for global and national action, fundamental to which will be improved access to these medicines for affected communities across the world (Box 1).

Yet, despite these achievements, the number of local community organisations and NGOs involved in the hepatitis arena at the country level remains limited. While some organisations that have traditionally had an HIV focus have shifted towards including viral hepatitis as a natural extension of their work on blood-borne infections and key affected populations, civil society organisations are often under-staffed, poorly funded and face the technical challenges of having to understand increasingly complex legal and regulatory barriers to drug access.

Policy considerations to improve HCV treatment access across the Asia-Pacific

Domestic, regional and international policy can provide a platform for addressing access to DAAs in the Asia-Pacific. Given the current global economic climate, it appears that the establishment of any new funding organisations is unlikely. Consequently, funding for HCV treatment will have to come from existing public health support mechanisms and domestic health insurance funds or individuals themselves will be forced to pay. There are several specific mechanisms that could be employed to address these high prices beyond regular market dynamics. The first is voluntary licensing. So far, only one proprietary pharmaceutical manufacturer has issued their own voluntary licensing schemes including 101 countries (Gilead Sciences Inc, 2015 #28810), which allows licensed generic manufacturing to occur at much reduced prices. Generic sofosbuvir is now available to those countries through Indian manufacturers at around US$300 per month of medicines. A list of currently available manufacturers, distributors and prices is shown in Table 1 [28]. International voluntary licensing agreements for HIV medicines may be an example for HCV medicines. Such agreements for antiretrovirals have been co-ordinated through the Medicines Patent Pool (MPP), an organisation that facilitates access to low price medicines through voluntary licensing and patent pooling. While new HCV medicines are not yet available through the MPP, some hepatitis B virus medicines can be accessed through their agreements. Other mechanisms to create access such as compulsory licensing are available through flexibilities inherent in current trade agreements (e.g. the Trade-related Aspects of Intellectual Property Rights or TRIPS agreement), but they are inconsistently used by governments.

In May 2015, six DAAs were added to the WHO Model Essential Medicines List (EML), including daclatasvir, simprevir and sofosbuvir, and the combinations of ledipasvir and sofosbuvir, and ombitasvir and paritvaprevir and ritonavir with or without dasabuvir.

### Box 1. Glasgow Declaration on Hepatitis 2015

Because there are 400 million people living with hepatitis B or hepatitis C infection with no country/region unaffected,

Because there is a lack of global awareness and most persons with hepatitis remain undiagnosed,

Because 1.4 million people die every year from complications of viral hepatitis yet most of these deaths can be prevented,

Because there are highly effective measures to prevent new hepatitis B and C infections and highly effective treatments that can suppress hepatitis B virus replication and cure hepatitis C infection, because universal access to prevention, diagnosis, care and treatment is a human right and promoting access to and affordability of these services is the responsibility of all stakeholders,

The participants of the inaugural World Hepatitis Summit believe it is possible and essential to set as a goal the elimination of both hepatitis B and C as public health concerns. We therefore call upon governments in all jurisdictions to develop and implement comprehensive, funded national hepatitis plans and programmes in partnership with all stakeholders and in line with the World Health Assembly Resolution 67.6 and, in collaboration with the World Health Organization, to define and agree on realistic yet aspirational global targets for prevention, testing, diagnosis, care and treatment.

### Table 1. Availability and pricing of generic sofosbuvir from manufacturers in India (updated 10 September 2015) [28]

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<tr>
<th>Marketing company</th>
<th>Brand name</th>
<th>Gilead licensee</th>
<th>Manufacturer</th>
<th>Printed price* (US$)</th>
<th>Market price* (US$)</th>
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<td>3 Cipla Limited</td>
<td>Hepcivir</td>
<td>Yes</td>
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<td>4 Dr Reddy’s Laboratories</td>
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<td>5 Emcure Pharmaceuticals Limited</td>
<td>Spegra</td>
<td>No</td>
<td>Natco Pharma Limited</td>
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<td>6 Hetero Healthcare Limited</td>
<td>Sofovir</td>
<td>Yes</td>
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<td>7 Mylan Pharmaceuticals Private Limited</td>
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<td>8 Mylan Pharmaceuticals Private Limited</td>
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<td>9 Natco Pharma Limited</td>
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<td>13 Aurobindo Pharma</td>
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<td>14 Laurus Laboratories</td>
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<td>15 Sequent</td>
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* Printed prices were obtained from bottle labels. Market prices are based on community procurement costs in Northeast India. Prices in other locations and through other suppliers may differ. All prices are for one 28-pill bottle and in approximate US$ (1 US$=62 Indian Rupees). TBD: to be determined, N/A: not applicable.
Countries should be encouraged to also include these DAAs in their national essential medicines lists as a first step to facilitate access, independent of price negotiations.

Globally, universal access to healthcare is an agreed priority. While there are a number of public, private and mixed models of financing healthcare, strategies to incorporate financing of HCV medications into domestic insurance schemes should be a priority. HCV treatment in the context of DAAs has a relatively short duration (e.g. under 6 months) and is highly effective, and so could conceivably be a one-in-a-lifetime treatment. Although post-acute re-infection is possible, this is less likely than in the case of primary infection [29]. Phased implementation of HCV treatment by treating those who are sickest first (such as those with F3–4 liver fibrosis), before expanding treatment to others would also reduce the initial budgetary impact of incorporating HCV treatment in health insurance schemes.

HCV/HIV co-infection and the availability of new DAAs

Data on the effectiveness of HCV/HIV co-infection treatment with DAAs is now becoming available. Although most trials to date have included only HIV-positive individuals with high (e.g. >500 cells/μL) CD4 cell counts, HIV infection does not appear to reduce the efficacy of DAAs. While this is promising, drug–drug interactions between DAAs and antiretrovirals are less clear. Nevertheless, HIV-positive patients should be a priority population for treatment access, as HCV infection is becoming an increasingly important contributor to mortality in HIV infection [30–32]. National HIV clinical guidelines across the region need to be updated to incorporate HCV treatment as a component of routine care and HIV co-infection management. As national health programmes begin to include HCV treatment, particular consideration must be given to addressing the stigma and systematic discrimination against PWID in healthcare settings that could be barriers to accessing HCV services as they have been to HIV services. PWID are the group most affected by HCV/HIV co-infection, but are likely to miss out on treatment opportunities for both infections unless negative perceptions, and discriminatory policies and practices can be effectively addressed.

Conclusion

New options in HCV treatment are stirring substantial excitement across the world for the potential for global HCV cure. With several DAA combination regimens on the market and in the pipeline, the future seems brighter than ever. However, in the Asia-Pacific – the region with the world’s largest numbers of people living with viral hepatitis – access to these new medications is extremely limited due to high prices and slow regulatory approval mechanisms. Stigma and discrimination, and poor hepatitis treatment literacy among affected communities and primary-care providers also contribute to reduced demand for and access to these new effective medicines. Overcoming these barriers will require concerted efforts by all stakeholders. International leadership is urgently needed to drive these policy and practice changes. Until we see these goals become realities, HCV-associated mortality will continue to climb, and those most in need in the Asia-Pacific will miss out on this revolution.

References


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