Direct-acting antiviral therapies for hepatitis C infection: global registration, reimbursement, and restrictions

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Direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection have delivered high response rates (>95%) and simplified the management of HCV treatment, permitting non-specialists to manage patients without advanced liver disease. We collected and reviewed global data on the registration and reimbursement (government subsidised) of HCV therapies, including restrictions on reimbursement. Primary data collection occurred between Nov 15, 2021, and July 24, 2023, through the assistance of a global network of 166 HCV experts. We retrieved data for 160 (77%) of 209 countries and juristrictions. By mid-2023, 145 (91%) countries had registered at least one of the following DAA therapies: sofosbuvir–velpatasvir, sofosbuvir–velpatasvir–voxilaprevir, glecaprevir–pibrentasvir, sofosbuvir–daclatasvir, or sofosbuvir. 109 (68%) countries reimbursed at least one DAA therapy. Among 102 low-income and middle-income countries (LMICs), 89 (87%) had registered at least one HCV DAA therapy and 53 (52%) reimbursed at least one DAA therapy. Among all countries with DAA therapy reimbursement (n=109), 66 (61%) required specialist prescribing, eight (7%) had retreatment restrictions, seven (6%) had an illicit drug use restriction, five (5%) had an alcohol use restriction, and three (3%) had liver disease restrictions. Global access to DAA reimbursement remains uneven, with LMICs having comparatively low reimbursement compared with high-income countries. To meet WHO goals for HCV elimination, efforts should be made to assist countries, particularly LMICs, to increase access to DAA reimbursement and remove reimbursement restrictions—especially prescriber-type restrictions—to ensure universal access.

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Introduction

An estimated 57 million people are living with chronic hepatitis C virus (HCV) worldwide.[1] HCV infection is associated with severe liver-related morbidity and mortality, resulting in a substantial global health burden.[2,3] In high-income countries, HCV transmission primarily occurs through contaminated injecting equipment among people who inject drugs. In low-income and middle-income countries (LMICs), although most HCV transmission occurs in health-care settings (eg, because of a scarcity of sterilised medical equipment), transmission via injection drug use is increasingly common.[4–7] WHO has set targets to eliminate viral hepatitis as a global public health threat by 2030, including diagnosing at least 90% of people with HCV and treating at least 80% of people diagnosed with HCV.[8] The absolute targets set by WHO strive to reduce annual HCV incidence to no more than 5 per 100 000 population (≤2 per 100 people who inject drugs) and annual mortality to no more than 2 per 100 000 population.[9] Few countries are currently on track to meet WHO targets,[10] underscoring the urgent requirement for governments to respond more effectively.

All-oral direct-acting antiviral drugs (DAAs) with response rates of greater than 95% have revolutionised HCV management, leading to declines in liver-related morbidity and mortality.[11–13] Due to the high list price of DAA therapies, many countries initially prioritised HCV treatment for people with severe liver disease. In 2018, research into reimbursement restrictions on DAA therapies in countries in the EU and European Economic Area (n=35) found that nearly half (46%) had fibrosis stage restrictions (≥F2; METAVIR score or equivalent).[14] Most European countries or jurisdictions (83%) also had prescriber restrictions, limiting DAA prescribing to infectious disease specialists, hepatologists, and gastroenterologists.[14] In 2015, a USA-based study (42 states plus the District of Columbia) found that the majority of states limited DAA reimbursement to advanced fibrosis (74%; ≥F3) and specialist prescribing (69%) and also had drug and alcohol use restrictions (88%); however, many states eased these restrictions when DAAs costs were reduced.[15,16] Similarly, in 2016, research into reimbursement restrictions on DAA access in Canada found that the majority of provinces and territories had fibrosis stage restrictions (up to 92%, depending on the DAA), and nearly half had prescriber restrictions (up to 42%, depending on the DAA), many of which have since been removed.[17,18] To date, there has been little research into access to DAAs and reimbursement of DAA therapy globally, especially in LMICs. There has also been minimal research into restrictions on HCV retreatment after virological treatment failure or reinfection from engagement in high-risk behaviours (eg, the sharing of contaminated injecting equipment). In a meta-analysis comprising 36 studies,[19] the overall HCV reinfection rate among people who inject drugs was estimated at 5·9 per 100 person-years; hence, timely uptake of HCV retreatment is important to reduce HCV incidence and prevalence. Furthermore, many HCV policy studies focus on single countries or regions, missing an opportunity for multicountry analyses and comparisons. The aims of this Health Policy paper were to review the global registration status of HCV DAAs, the

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reimbursement of DAAs (government reimbursed, subsidised, or fee-free policy), and the presence and type of restrictions (prescriber type, liver disease stage, drug and alcohol use, and retreatment) on DAA reimbursement.

Methods

We reviewed global data on the registration and reimbursement of DAAs for HCV infection, including restrictions on reimbursement. Methods used in this study to assess reimbursement restrictions to DAAs were similar to those applied in previous studies in Canada, Europe, and the USA.[14,15,17] For this Health Policy paper, we focused on whether people living with HCV could access subsidised DAAs (originators or generics) via government reimbursement, subsidy, or a fee-free policy. We collected data on DAA access for people aged 18 years and older, given the lack of focus on the management of HCV treatment in children globally.[20]

Some LMICs accessed DAAs through a third-party agreement with a major international donor (eg, Global Fund to Fight AIDS, Tuberculosis and Malaria; or US President's Emergency Plan for AIDS Relief) or non-governmental organisation (eg, Médicins Sans Frontières). These funding circumstances were mostly limited to specific population groups (eg, providing HCV treatment without patient costs to people coinfected with HIV and HCV) rather than broad population access. Such circumstances are unstable in the long term due to changing donor priorities (eg, Médicins Sans Frontières no longer supplies DAAs to Cambodia).[21] In these cases, we did not categorise the country as having a formal DAA reimbursement structure. Given that major international donors are not heavily involved in HCV service funding,[4] we did not anticipate that funding from these donors would be common.

Between Aug 2, 2021, and Oct 29, 2021, an initial grey literature search was conducted, by ADM, ARW, AK, NB, DJ, and VD, using Google. Primary outcome data on the registration status of DAAs (generics or originators), whether these DAAs were reimbursed, and restrictions to accessing reimbursed DAAs were extracted from publicly available sources, including drug regulatory websites, online drug formularies, and HCV-related documentation, such as national HCV guidelines or HCV strategies. Data were recorded in a prepiloted and prestandardised database.

Next, to establish a network of global experts (primarily experts in HCV and HIV), we attempted to connect with in-country experts in the fields of infectious diseases, gastroenterology, hepatology, and addiction medicine. First, we used our existing HCV contacts to facilitate access to global experts working in the field. Second, we contacted in-country experts who had contributed to our previous work on HCV-related DAA reimbursement restrictions in Europe.[14] Third, where there was no previous collaboration, we identified potential global HCV and HIV experts from peer-reviewed publications available through PubMed. Finally, we used UN agencies, including regional WHO and UNAIDS offices, to facilitate in-country contacts. We aimed to have at least one in-country expert per country. Next, an email invite was sent (by JG) to the global network of experts to explain the purpose of the research. Most in-country experts were contacted in English, with a few contacted in French, Spanish, or Portuguese. If the in-country expert agreed to participate, the extracted in-country data and verified sources were provided to them. When an expert agreed to participate but did not respond to subsequent emails, they were reprompted twice, and if there was no response, another potential collaborator was contacted.

Where no country data had been found, we asked the in-country expert to facilitate access to official documentation related to primary study outcomes. The in-country experts were asked to provide verifiable sources, such as online drug formularies and reimbursement website links or documentation and other relevant documentation (eg, press releases from health ministries and essential medicines lists). If national clinical practice guidelines were not available, the in-country experts were asked to clarify which regional clinical practice guidelines their country used (eg, Asian Pacific Association for the Study of the Liver, European Association for the Study of the Liver, or WHO guidelines). When written documentation on HCV was unavailable, we confirmed the lack of availability with the in-country experts. As with previous research,[14] if the information of interest was not located in written documentation (eg, clinical practice guidelines) or in the expected online locations, this information was categorised as none stated. If no information could be found for a specific country (which was unlikely if we had access to an in-country expert), this information was categorised as no information. In-country experts were asked to provide written documentation in their country's language (or languages), which was translated using Google Translate. From Nov 15, 2021, to July 24, 2023, data were extracted from the provided documentation by ADM, ARW, and AK. The in-country experts were sent follow-up emails asking them to provide clarification of interpretation and verify recorded data in the tables and appendices.

Between Nov 15, 2021, and July 24, 2023, we contacted about 820 potential collaborators; of those contacted, 166 representing 160 countries and jurisdictions ultimately agreed to participate. This network of 166 collaborators, designated the Global HCV and HIV Treatment Restrictions Group (appendix pp 2–9), facilitated the collection and extraction of information from 160 (77%) of 209 countries. As with a previous review,[14] we reported separately on the jurisdictions of England, Northern Ireland, Scotland, and Wales. Svalbard and Jan Mayen were treated as separate jurisdictions from Norway, and Greenland as separate from Denmark. Regarding

See Online for appendix

population size, we received information from countries covering approximately 7·4 billion people, representing about 95% of the global population. Nearly all in-country experts were based within the country of interest. In June and July, 2023, we asked members of our collaborator network to validate their country data and provide any updates.

Primary outcome data on DAA registration status, reimbursement, and restrictions to access are presented globally and by region: east and southeast Asia, central Asia, south Asia, eastern Europe, western Europe, the Middle East and north Africa, sub-Saharan Africa, North America, Latin America, the Caribbean, Pacific Island Countries and Territories, and Australasia. Data based on country income classification (eg, LMICs)[22] are also presented.

Registration data were collected for sofosbuvir–velpatasvir, sofosbuvir–velpatasvir–voxilaprevir, glecaprevir–pibrentasvir, sofosbuvir, and daclatasvir. In the case of sofosbuvir and daclatasvir, we reported on sofosbuvir–daclatasvir combination therapy and sofosbuvir alone. Data collection was restricted to these DAAs to focus on pan-genotypic therapies, while recognising that sofosbuvir–daclatasvir or sofosbuvir alone might be more commonly used in LMICs. It was also possible to have a DAA that was registered but not marketed (eg, sofosbuvir in Czech Republic). In these circumstances, the DAA was categorised as registered.

Regarding reimbursement, we extracted data on the subsidising of DAA treatment. We did not record restrictions to DAAs through the private health insurance system. Most people who are impacted by HCV infection make up marginalised population groups who are economically disenfranchised (around 50% of the world's population have a daily salary <US$2, if employed at all), and our research aim was to characterise the proportion of global residents who could access DAAs regardless of income.[23]

Regarding restrictions to reimbursed DAAs, we recorded restrictions pertaining to prescriber type, liver disease staging, use of illicit drugs or alcohol, and retreatment. If patients were expected to meet the full DAA costs themselves, restriction data were not applicable (or collected), as patients could pay for DAAs without limitations (eg, liver disease stage restrictions). We added the category of not applicable to include these circumstances. For each country, we categorised restrictions as: restriction (DAA reimbursement limited by the restriction of interest); no restriction (DAA reimbursement not limited by the restriction of interest); none stated (DAA reimbursement available but no evidence of restriction of interest); restriction data unavailable (DAA reimbursement available but restriction data unknown); not applicable (DAA reimbursement not available); and no information (country not included in restriction analysis due to absence of reimbursement data).

Prescriber-type categories were restriction (ie, specialist only—physician prescription not permitted), no restriction, none stated, restriction data unavailable, not applicable, and no information. Countries that permitted non-specialists to prescribe were categorised as no restriction; in these cases, non-specialists able to prescribe DAAs might have had to complete a minimum level of education, with or without a training course, for example. In some countries, the implementation of health services is mandated by states or provinces (eg, Canada and the USA), rather than nationally. As noted in previous studies,[15,17] this form of implementation often results in considerable intracountry differences regarding DAA access (eg, specialist prescribing restrictions in some states but not others). For Canada and the USA, we categorised the restriction on the basis of how most provinces or states implemented the restriction (eg, if most states required specialist-only prescribing, the restriction was categorised as specialist only).

Liver disease staging categories were restriction (≥F1), no restriction, none stated, restriction data unavailable, not applicable, and no information. We noted when a minimum fibrosis stage (METAVIR score or equivalent) was required to enable access to reimbursed DAAs. We did not record whether certain procedures (eg, transient elastography) were required for liver disease assessment, because these data are mentioned infrequently in documentation.

Drug and alcohol use categories were restriction, no restriction, none stated, restriction data unavailable, not applicable, and no information. We recorded whether there were any mandatory drug and alcohol use restrictions (eg, drug or alcohol abstinence requirements). A requirement for patients to receive reimbursed HCV treatment from specific centres was categorised as no restriction, given that DAA access was still possible, albeit limited.

HCV DAA retreatment categories were restriction, no restriction, none stated, restriction data unavailable, not applicable, and no information. An example of a retreatment restriction is a limit on the number of times a patient could receive reimbursed HCV treatment. We did not differentiate between reimbursement policies that differed regarding the cause of reinfection (eg, treatment failure or risk behaviours).

ADM, ARW, AK, EBC, AW, and JG held regular meetings to review the interpretation and ultimate categorisation of data. When we could not verify the validity of the data retrieved from a specific country (eg, did not hear back from the in-country expert following a prompt), we deferred to the most recent written document available as the final source. Discrepancies were decided by consensus. All data and tables were organised in Microsoft Excel (version 2023).

Findings

Of the 160 countries from which we retrieved data, 145 (91%) had at least one HCV DAA (or combination of DAAs) registered: 122 (76%) countries had

Reimbursed
Not reimbursed
Reimbursement status unknown
✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
Eastern Europe					
Armenia*	✓	×	✓	×	×
Azerbaijan*	✓	×	×	✓	✓
Belarus*	✓	×	✓	×	✓
Bosnia and Herzegovina*	✓	×	✓	×	×
Bulgaria	✓	✓	✓	×	✓
Croatia	✓	✓	✓	×	✓
Czech Republic	✓	✓	✓	×	✓
Estonia	✓	✓	✓	×	×
Georgia*	✓	×	×	×	✓
Hungary	✓	✓	✓	×	✓
Latvia	✓	✓	✓	×	✓
Lithuania	✓	✓	✓	×	✓
Moldova*	×	×	✓	✓	✓
Poland	✓	✓	✓	×	✓
Romania	✓	✓	✓	×	✓
Russia	✓	×	✓	✓	✓
Slovakia	✓	✓	✓	×	✓
Svalbard and Jan Mayen	✓	✓	✓	×	✓
Ukraine*	✓	×	✓	✓	✓
Western Europe					
Albania*	✓	×	✓	×	×
Andorra					
Austria	✓	✓	✓	✓	✓
Belgium	✓	✓	✓	×	✓
Denmark	✓	✓	✓	×	✓
England	✓	✓	✓	×	✓
Finland	✓	✓	✓	×	✓
France	✓	✓	✓	×	✓
Germany	✓	✓	✓	✓	✓
Greece	✓	✓	✓	×	✓
Greenland	✓	✓	✓	×	✓
Iceland	✓	✓	×	×	✓
Ireland	✓	✓	✓	×	✓
Italy	✓	✓	✓	×	✓
Liechtenstein	✓	✓	✓	×	✓

(Figure 1 continues on next page)

Reimbursed
Not reimbursed
Reimbursement status unknown
✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
Luxembourg	✓	✓	✓	×	✓
Malta	✓	✓	×	×	×
Monaco					
Montenegro*	✓	×	✓	×	×
Netherlands	✓	✓	✓	✓	✓
North Macedonia*	×	×	×	×	×
Norway	✓	✓	✓	×	✓
Northern Ireland	✓	✓	✓	×	✓
Portugal	✓	✓	✓	×	✓
San Marino					
Scotland	✓	✓	✓	×	✓
Serbia*	✓	×	✓	×	✓
Slovenia	✓	✓	✓	×	✓
Spain	✓	✓	✓	×	✓
Sweden	✓	✓	✓	×	✓
Switzerland	✓	✓	✓	×	✓
Wales	✓	✓	✓	×	✓
East and southeast Asia					
Brunei	✓	×	✓	×	×
Cambodia*	×	×	×	✓	✓
China*	✓	✓	✓	✓	✓
Indonesia*	✓	×	×	✓	✓
Japan	✓	×	✓	✓	✓
Laos*	✓	×	×	✓	✓
Malaysia*	✓	×	×	✓	✓
Mongolia	✓	×*	×	✓	✓
Myanmar*	×	×	×	✓	✓
North Korea*					
Philippines*	✓	×	×	✓	✓
Singapore	✓	✓	✓	×	×
South Korea	✓	✓	✓	✓	✓
Taiwan	✓	✓	✓	×	✓
Thailand*	✓	×	×	×	✓
Timor-Leste*	✓	×	×	×	×
Viet Nam*	✓	×	×	✓	✓

(Figure 1 continues on next page)

Reimbursed
Not reimbursed
Reimbursement status unknown

✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
South Asia					
Afghanistan*	×	×	×	✓	✓
Bangladesh*	✓	×	✓	✓	✓
Bhutan*	✓	×	×	×	✓
India*	✓	×	×	✓	✓
Iran*	✓	×	×	✓	✓
Maldives*	✓	×	×	×	✓
Nepal*	✓	×	×	×	✓
Pakistan*	✓	×	×	✓	✓
Sri Lanka*					
Central Asia					
Kazakhstan*	✓	×	×	✓	✓
Kyrgyzstan*	✓	×	×	✓	✓
Tajikistan*	✓	×	×	✓	✓
Turkmenistan*					
Uzbekistan*	✓	×	×	✓	✓
Caribbean					
Antigua and Barbuda					
Bahamas					
Barbados					
Bermuda					
Cuba*	×	×	×	×	✓
Dominica*					
Dominican Republic*	✓	✓	×	✓	✓
Grenada*					
Haiti*	×	×	×	✓	✓
Jamaica*	✓	×	×	×	×
Puerto Rico	✓	✓	✓	×	✓
Saint Kitts and Nevis					
Saint Lucia*					
Saint Vincent and the Grenadines*	×	×	×	×	×
Trinidad and Tobago	×	×	×	×	×
Latin America					
Argentina*	✓	✓	✓	✓	✓
Belize*					
Bolivia*	×	×	×	✓	✓

(Figure 1 continues on next page)

Reimbursed Not reimbursed Reimbursement status unknown ✓ Registered × Not registered	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
Brazil*	✓	✓	✓	✓	✓
Chile	✓	✓	×	×	×
Colombia*	✓	×	×	✓	✓
Costa Rica*					
Ecuador*	×	×	×	×	✓
El Salvador*					
French Guiana					
Guatemala*	✓	×	×	×	×
Guyana*	✓	×	×	✓	✓
Honduras*					
Mexico*	✓	×	✓	×	✓
Nicaragua*					
Panama*					
Paraguay*					
Peru*	✓	×	✓	×	✓
Suriname*					
Uruguay	✓	×	✓	✓	✓
Venezuela*	×	×	×	×	✓
North America					
Canada	✓	✓	✓	×	✓
USA	✓	✓	✓	×	✓
Pacific Island Countries and Territories					
American Samoa					
Cook Islands†					
Federated States of Micronesia*					
Fiji*	×	×	×	×	×
French Polynesia					
Guam					
Kiribati*					
Marshall Islands*					
Nauru*					
New Caledonia					
Palau*					
Papua New Guinea*	×	×	×	×	×
Samoa*					
Solomon Islands*					

(Figure 1 continues on next page)

Reimbursed
Not reimbursed
Reimbursement status unknown
✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
Tonga*	×	×	×	×	×
Tuvalu*					
Vanuatu*					
Australasia					
Australia	✓	✓	✓	×	×
New Zealand	✓	✓	✓	×	✓
Middle East and north Africa					
Algeria*	✓	×	×	✓	✓
Bahrain	✓	×	✓	×	✓
Cyprus	✓	✓	✓	×	✓
Egypt*	✓	✓	×	✓	✓
Iraq*					
Israel	✓	✓	✓	×	×
Jordan*	✓	×	×	✓	✓
Kuwait	✓	✓	✓	×	×
Lebanon*	✓	✓	✓	✓	✓
Libya*	✓	✓	×	✓	✓
Morocco*	✓	×	×	✓	✓
Occupied Palestinian territory*	×	×	×	×	×
Oman	✓	×	×	✓	✓
Qatar					
Saudi Arabia	✓	✓	✓	✓	✓
Sudan*	×	×	✓	×	×
Syria*					
Tunisia*	×	×	×	×	✓
Türkiye*	×	✓	✓	×	✓
United Arab Emirates	✓	✓	✓	×	✓
Yemen*					
Western Sahara*					
Sub-Saharan Africa					
Angola*	×	×	×	×	×
Benin*	✓	×	×	✓	✓
Botswana*	✓	×	×	×	✓
Burkina Faso*	✓	×	×	✓	✓
Burundi*	✓	×	×	✓	✓
Cameroon*	✓	×	×	✓	✓

(Figure 1 continues on next page)

Reimbursed
Not reimbursed
Reimbursement status unknown
✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
Cabo Verde*					
Central African Republic*					
Chad*	✓	×	×	✓	✓
Comoros*	×	×	×	✓	✓
Cote d'Ivoire*	✓	×	×	×	×
DR Congo*	×	×	×	✓	✓
Djibouti*					
Equatorial Guinea*					
Eritrea*	✓	✓	✓	✓	✓
Eswatini*	×	×	×	×	×
Ethiopia*	✓	×	×	✓	✓
Gabon*	×	×	×	✓	✓
The Gambia*	×	×	×	×	×
Ghana*	×	×	×	×	×
Guinea*	✓	✓	✓	✓	✓
Guinea-Bissau*	✓	×	✓	✓	✓
Kenya*	✓	×	×	✓	✓
Lesotho*					
Liberia*	×	×	×	✓	✓
Madagascar*	✓	×	×	×	✓
Malawi*	✓	×	×	✓	✓
Mali*	×	×	×	×	✓
Mauritania*	×	×	×	✓	✓
Mauritius*	✓	×	×	×	×
Mozambique*	✓	×	✓	✓	✓
Namibia*	×	×	×	×	✓
Niger*					
Nigeria*	✓	×	×	✓	✓
Republic of the Congo*					
Rwanda*	✓	✓	×	✓	✓
São Tomé and Príncipe					
Senegal*					
Seychelles					
Sierra Leone*					
Somalia*	×	×	×	✓	✓
South Africa*	✓	×	×	×	×

(Figure 1 continues on next page)

Reimbursed
Not reimbursed
Reimbursement status unknown
✓ Registered
× Not registered

	Sofosbuvir–velpatasvir	Sofosbuvir–velpatasvir–voxilaprevir	Glecaprevir–pibrentasvir	Sofosbuvir–daclatasvir	Sofosbuvir
South Sudan*	×	×	×	×	✓
Togo*	✓	×	×	✓	✓
Uganda*	✓	×	×	✓	✓
Tanzania*	✓	×	×	✓	✓
Zambia*	×	×	×	✓	✓
Zimbabwe*	×	×	×	✓	✓

Figure 1: **Registered and reimbursed direct-acting antiviral drugs for HCV infection by country**
Blank cells indicate registration status unknown. *Designated as low-income and middle-income country or territory as defined by the Development Assistance Committee of the Organisation for Economic Cooperation and Development; effective for reporting on 2022 and 2023 flows.[22] †There is no regulatory authority for medicines in the Cook Islands; instead, regulations allow the import of medicines that have been approved by recognised regulatory authorities, currently those of New Zealand, Australia, Canada, the USA, Europe, and the UK (Orange A, Cook Islands Ministry of Health, personal communication).

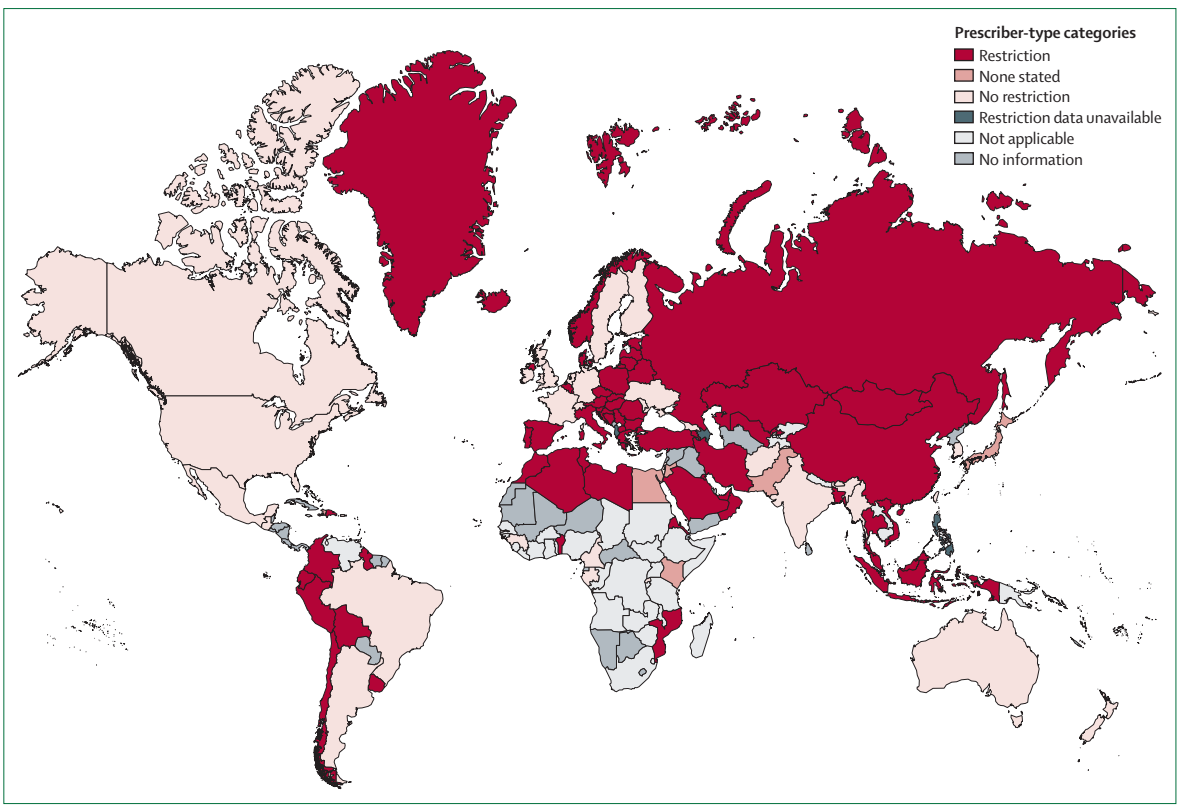

Figure 2: **Prescriber-type restrictions on reimbursement of direct-acting antiviral drugs for patients with HCV infection by country**
Maps were made with Tableau (version 2023.1); base maps were sourced from OpenStreetMap and Mapbox.

sofosbuvir–velpatasvir, 61 (38%) had sofosbuvir–velpatasvir–voxilaprevir, 73 (46%) had glecaprevir–pibrentasvir, 68 (43%) had sofosbuvir–daclatasvir, and 126 (79%) had sofosbuvir. Some regions had fewer DAAs registered than others—eg, none of the countries in the Pacific Island Countries and Territories had at least one DAA registered (figure 1). Among LMICs (n=102), 89 (87%) had at least one HCV DAA registered: 66 (65%) countries had sofosbuvir–velpatasvir, 11 (11%) had sofosbuvir–velpatasvir–voxilaprevir, 21 (21%) had glecaprevir–pibrentasvir, 59 (58%) had sofosbuvir–daclatasvir, and 78 (76%) had sofosbuvir.

Among the 160 countries with available data, 109 (68%) reimbursed at least one DAA: 94 (59%) reimbursed

sofosbuvir–velpatasvir, 52 (33%) reimbursed sofosbuvir–velpatasvir–voxilaprevir, 65 (41%) reimbursed glecaprevir–pibrentasvir, 43 (27%) reimbursed sofosbuvir–daclatasvir, and 72 (45%) reimbursed sofosbuvir. Some regions had considerably more reimbursement than others—eg, of countries with available information, all 19 (100%) countries in eastern Europe had access to reimbursed DAAs, compared with two of four countries in central Asia and nine of 36 countries in sub-Saharan Africa (figure 1). Among LMICs (n=102), 53 (52%) had reimbursed at least one DAA: 43 (42%) reimbursed sofosbuvir–velpatasvir, nine (9%) reimbursed sofosbuvir–velpatasvir–voxilaprevir, 13 (13%) reimbursed glecaprevir–pibrentasvir, 35 (34%) reimbursed sofosbuvir–daclatasvir, and 41 (40%) reimbursed sofosbuvir. A few countries had DAAs reimbursed but not registered—eg, sofosbuvir–velpatasvir in Moldova and North Macedonia, sofosbuvir–velpatasvir–voxilaprevir in Azerbaijan, and glecaprevir–pibrentasvir in Azerbaijan and the Cook Islands (provided through an arrangement with New Zealand). Sofosbuvir–daclatasvir was listed as reimbursed but was no longer registered in Ireland, Mexico, Norway, or Svalbard and Jan Mayen.

Among the 109 countries with reimbursed DAAs, 66 (61%) had a specialist-only restriction, of which nearly half (n=31) were LMICs (appendix p 12). 35 (32%) had no restrictions, five (5%) had none stated, and three (3%) had no restriction data available (Albania, Azerbaijan, and the Philippines; figure 2). In some countries, such as Guatemala, prescribing by primary care physicians was permitted, but treatment was only available at public HIV centres managed by HIV specialists. Thus, in practice, DAA prescribing among primary care physicians was not common.

Of the 109 countries with reimbursed DAAs, three (3%; including one LMIC) had a liver fibrosis disease stage requirement of at least F1 (ie, minimal fibrosis or higher), 93 (85%) had no liver fibrosis restriction, ten (9%) had none stated, and three (3%) had no restriction data available (Albania, Libya, and the Philippines; figure 3). The three countries with listed fibrosis stage requirements were Latvia (≥F1), Lithuania (≥F2), and Thailand (≥F2). In several countries (eg, Colombia, Croatia, Eritrea, Mozambique, Peru, Russia, Ukraine, and Uzbekistan), written documentation stated that ministries would implement liver disease staging requirements if there was ever a short supply of DAAs or that they prioritised people with higher liver disease stage (≥F3) for HCV treatment.

Seven (6%) of the 109 countries with reimbursed DAAs (including four LMICs) had drug use restrictions, 77 (71%) had no drug use restrictions, 21 (19%) had none stated, and four (4%) had no restriction data available (Albania, Bolivia, China, and the Philippines; figure 4). There were five (5%) countries (including three LMICs)

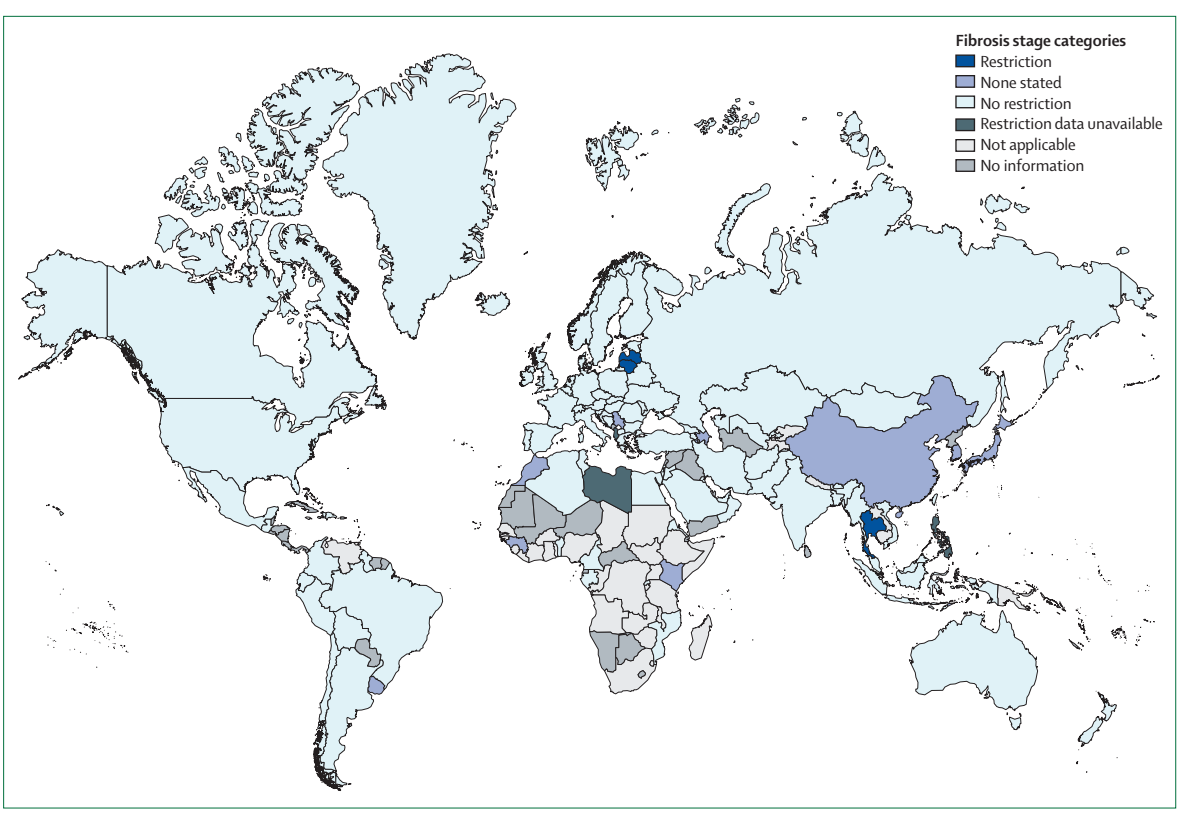

Figure 3: **Liver fibrosis disease stage restrictions on reimbursement of direct-acting antiviral drugs for patients with HCV infection by country**
Maps were made with Tableau (version 2023.1); base maps were sourced from OpenStreetMap and Mapbox.

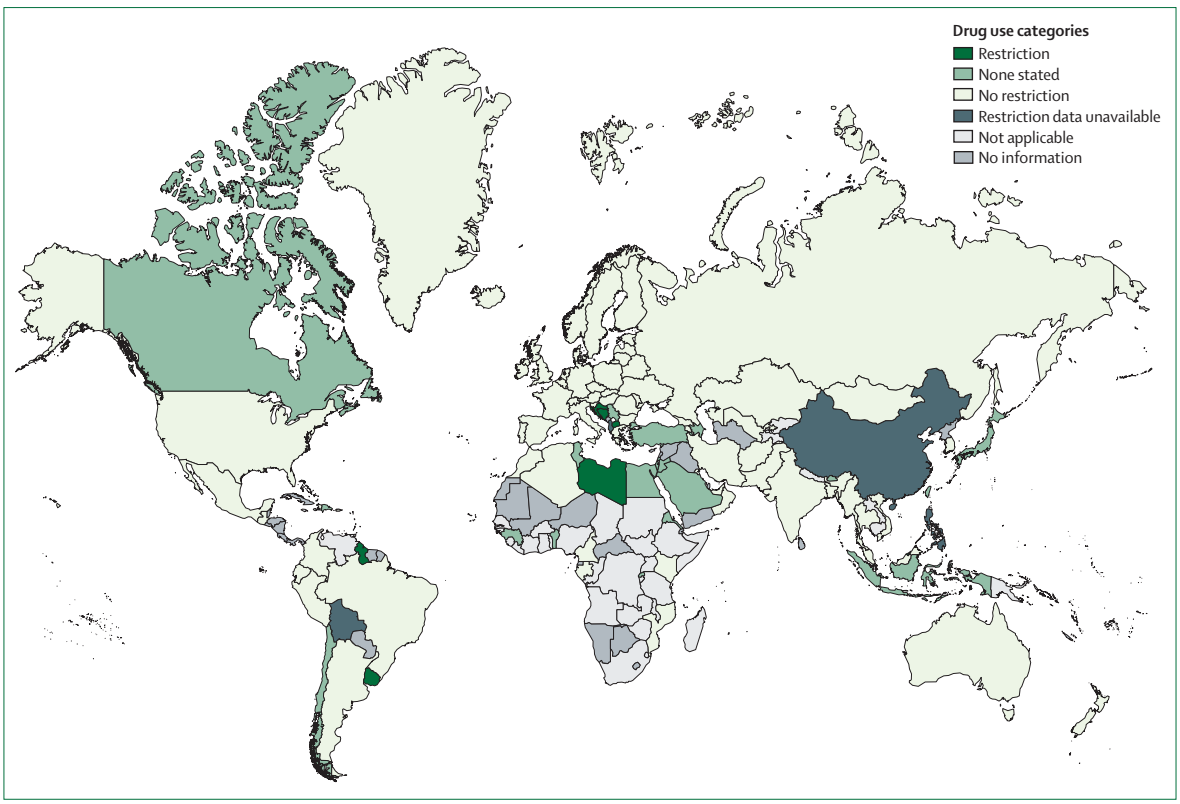

Figure 4: **Illicit drug use restrictions on reimbursement of direct-acting antiviral drugs for patients with HCV infection and recent drug dependence by country**
Maps were made with Tableau (version 2023.1); base maps were sourced from OpenStreetMap and Mapbox.

with alcohol use restrictions, 68 (62%) with no alcohol use restrictions, 31 (28%) with none stated, and five (5%) had no restriction data available (Albania, Bangladesh, Bolivia, China, and the Philippines; figure 5). Restrictions included patient abstinence from drug and alcohol use, enrolment in an opioid agonist treatment programme or substance use rehabilitation programme, or evaluation by a mental health provider before DAA initiation (Bosnia and Herzegovina, North Macedonia, Brunei, Croatia, Guyana, Libya, and Uruguay; appendix p 10).

Eight (7%) of the 109 countries (including four LMICs) had HCV retreatment restrictions, 76 (70%) had no restrictions, 21 (19%) had none stated, and four (4%) had no restriction data available (Albania, China, Libya, and the Philippines; figure 6). Restrictions included limiting retreatment cycles (Puerto Rico, Taiwan, and Türkiye) or partly reimbursing retreatment (South Korea). Bosnia and Herzegovina provided retreatment to people who injected drugs on a case-by-case basis. North Macedonia, Myanmar, and Uruguay did not reimburse retreatment (appendix p 11). Some country documentation provided instructions to practitioners regarding retreatment in the case of virological failure (eg, Pakistan and Kazakhstan) but lacked guidance for retreatment in the event of reinfection from high-risk behaviours. Country guidance could also be province specific, as in the case of Canada, which does not have a national retreatment policy (here, most residents had no restrictions to reimbursed retreatment or were treated on a case-by-case basis; appendix p 12). In some countries, such as Canada, although there were no official restrictions to reimbursed retreatment, there could be additional barriers to accessing it (eg, additional paperwork and communication with the relevant insurance and health authorities to establish the need for retreatment).

Discussion

We retrieved data for 160 countries regarding the registration and reimbursement of DAAs for HCV therapy and restrictions on reimbursed DAAs worldwide. 145 (91%) countries had at least one DAA registered, and 109 (68%) reimbursed at least one DAA therapy. Among 102 LMICs, 89 (87%) had at least one DAA registered, and 53 (52%) reimbursed at least one DAA therapy. 66 (61%) of all countries had a prescriber-type restriction, three (3%) had liver disease stage restrictions, seven (6%) had drug use restrictions, five (5%) had alcohol use restrictions, and eight (7%) had retreatment restrictions. Despite a recent trend towards removing restrictions to reimbursed DAAs,[14,15,17] more work is needed to increase global access to these therapies and reach WHO targets.

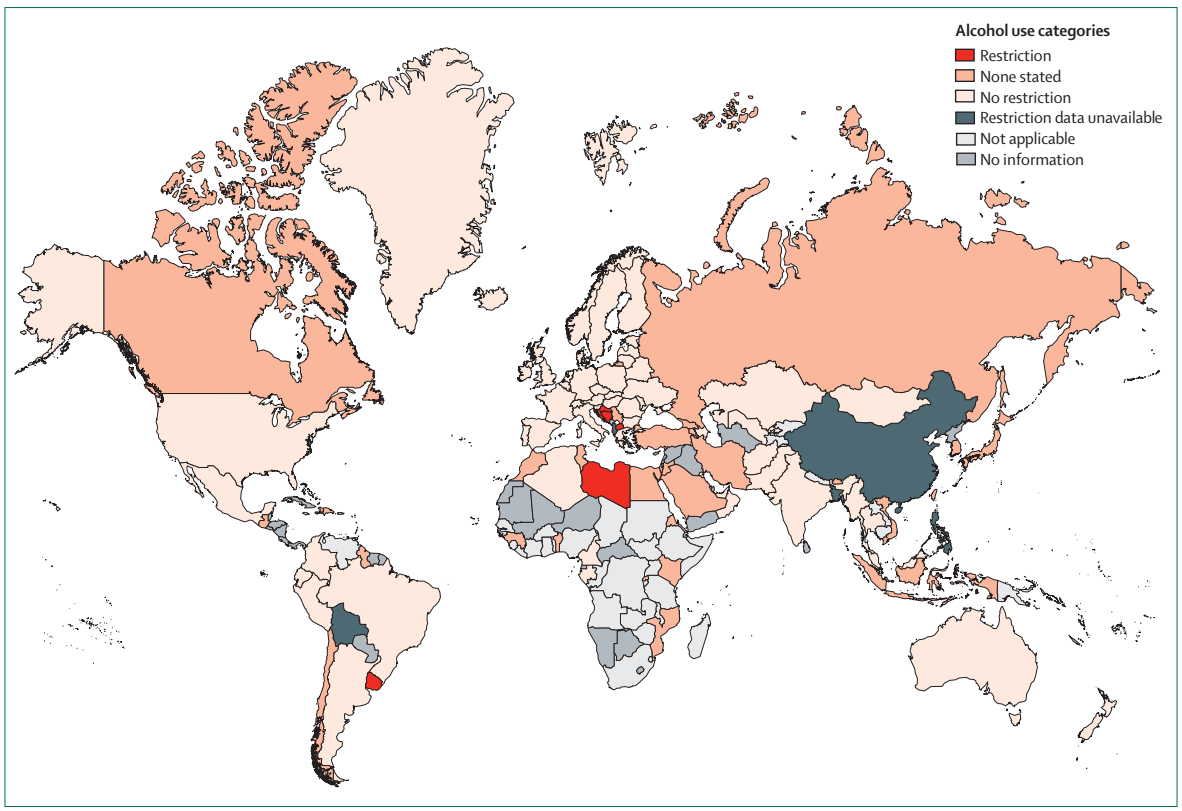

Figure 5: **Alcohol use restrictions on reimbursement of direct-acting antiviral drugs for patients with HCV infection and recent alcohol dependence by country**

Maps were made with Tableau (version 2023.1); base maps were sourced from OpenStreetMap and Mapbox.

Our findings suggest suboptimal levels of DAA reimbursement among countries where these treatments are registered, with considerable variation in regional access. Compared with all other countries, fewer reimbursed DAAs were provided in central Asia, the Caribbean, Pacific Island Countries and Territories, and sub-Saharan Africa. Although the development and approval timelines varied for DAAs, our findings illustrate disparities in reimbursement, with LMICs particularly disadvantaged. Our findings also provide a baseline from which further research could explore additional indicators to delineate DAA access. For example, some HCV treatment was solely provided in urban-based, specialised HIV centres; thus, additional research primarily focusing on optimisation of DAA implementation is merited.

Our data indicate that prescriber restrictions were the most common DAA restriction. 66 (61%) countries implemented specialist-only prescribing, consistent with findings from a European study.[14] This restriction reduces the proportion of available prescribers and requires patients to receive treatment from a specialist centre (often hospital based). This restriction is a major barrier for marginalised population groups (eg, people who inject drugs), who are more likely to experience stigma in health-care settings and avoid attending hospital-based centres, and for people residing in remote areas, who live further away from specialists.[5,24] There are some specialist prescribing pathways that seem to elicit minimal patient burden—eg, in Norway, a hospital-based specialist submits an electronic prescription to a community-based practitioner, avoiding the need for the patient to attend the hospital. Nonetheless, increasing task sharing of HCV testing and treatment in non-specialised centres (eg, primary care centres) would broaden access.[8,25] A review of 142 studies involving 34 countries found that non-specialists managing HCV-related care achieved similar HCV cure responses to specialists, providing evidence for task sharing.[26–28] Practitioners who take on DAA prescribing have also reported professional benefits (eg, professional fulfilment).[29] Nonetheless, even when countries permit general practitioners to prescribe DAAs, this practice might be uncommon, as providers might be unaware of the change in clinical guidelines,[25] indicating that ongoing, widespread awareness campaigns are needed.

Three countries required evidence of liver fibrosis as a prerequisite for reimbursing DAAs. The removal or lack of liver disease stage restrictions in most countries—previously, nearly three-quarters (74%) of US states and nearly half (46%) of European countries had fibrosis stage restrictions[14,15]—is likely to be the result of reduced

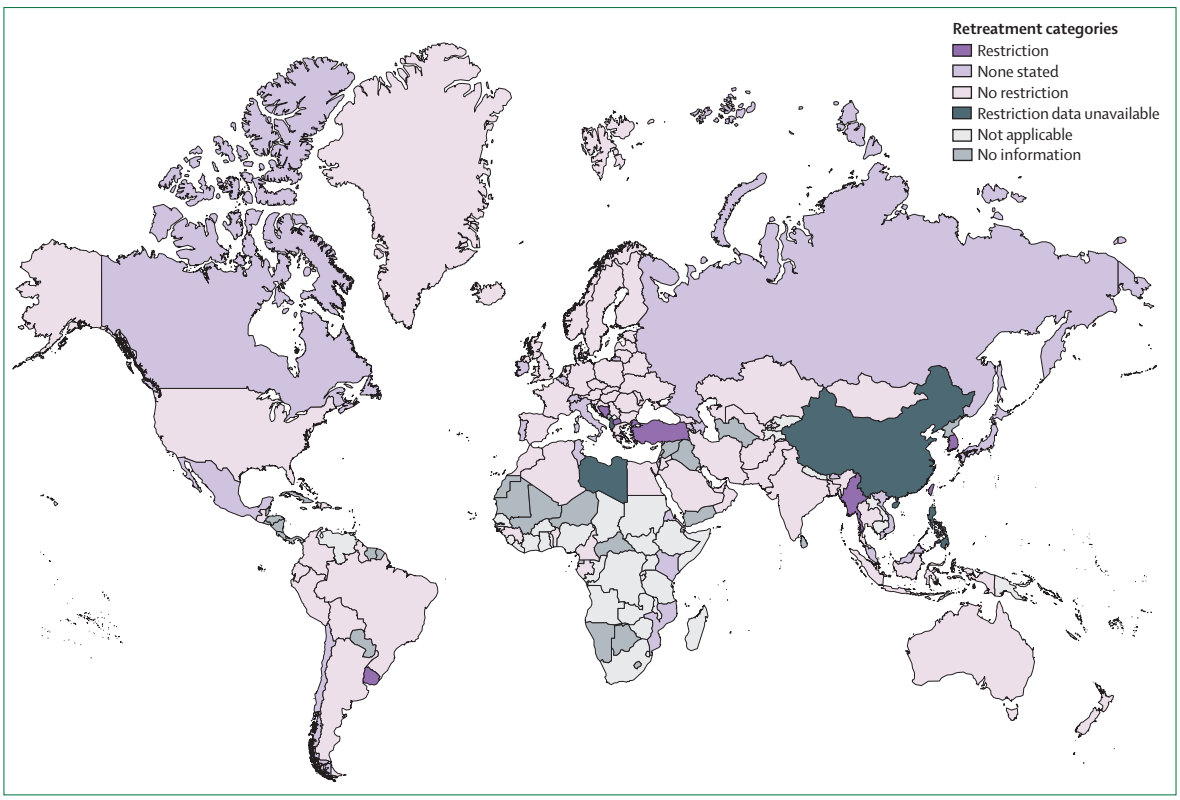

Figure 6: **Retreatment restrictions on reimbursement of direct-acting antiviral drugs for patients with HCV infection by country**
Maps were made with Tableau (version 2023.1); base maps were sourced from OpenStreetMap and Mapbox.

DAA prices.[30,31] Patients are no longer required to attend an additional appointment to receive a direct liver disease assessment (eg, transient elastography) before DAA initiation, unless compensated or decompensated liver cirrhosis is indicated through an indirect liver assessment (eg, blood test). Allowing indirect liver disease assessments has also meant that LMICs with limited health budgets and low numbers of trained personnel—and clinics beyond urban areas—can implement simplified HCV test and treat care models, enhancing patient access to care.[30]

Seven countries had illicit drug use restrictions, and five had alcohol use restrictions. People who use illicit drugs or alcohol can adhere to DAA therapy[32,33] and should be offered HCV treatment without delay, in accordance with WHO recommendations.[34] The intention of the listed restriction criteria might be to offer holistic HCV-related care, but these requirements contrast with WHO's call for simplified care models[25] and are likely to exacerbate health inequities.[35] Such restrictions should be removed. Lastly, regarding the available data, a sizeable proportion of countries did not have information on drug and alcohol use restrictions. Countries should provide clearer guidance in their national HCV treatment policies and guidelines.

Eight countries had restrictions on patients accessing HCV retreatment. Compared with retrieving information on other restrictions, retreatment documentation was more challenging to interpret. Country documentation frequently stated that retreatment was permitted for virological failure, but retreatment for reinfection due to high-risk behaviour was not often stated or evident. A few countries limited retreatment cycles. HCV retreatment information should be stated clearly in national policies, clinical guidance documents, and health insurance forms. Improved guidance would minimise the administrative burdens on providers, making it clearer that retreatment is permitted and alleviating practitioner hesitation about offering HCV treatment or retreatment to people who inject drugs, who are highly likely to adhere to treatment and retreatment.[36–39] Timely uptake of initial treatment and retreatment will be important for decreasing HCV prevalence and incidence globally.[40,41] Increased coverage of harm reduction services worldwide[42,43] would permit more integrated HCV harm reduction services models, helping to increase HCV treatment and retreatment uptake among people who inject drugs.[44,45] Lastly, although some countries permitted retreatment, they did not have many therapies registered, so retreatment options were limited. Although some preliminary evidence has shown high cure response rates (>90%) in LMICs when second-line HCV DAAs for retreatment are used, applying a health

equity lens, our broader goal should be to increase access to sofosbuvir–velpatasvir–voxilaprevir globally.[46]

Compared with other infectious diseases, global leadership and financial backing is lacking for HCV.[47,48] High DAA costs continue to limit access because not all countries have a universal health-care system willing or able to cover costs, indicating a need for more innovative financing models (eg, public–private partnerships).[4,48–50] Some countries have the capacity to manufacture their own generic versions of HCV therapies (eg, China, India, Egypt, and Russia), and, notably, some LMICs have widespread access to generics (eg, sofosbuvir–daclatasvir was available for US$60 per 12-week DAA regimen in Rwanda in 2019).[47] A few LMICs in this study were receiving DAA supplies from an international non-governmental organisation or via funding from the Global Fund, which could become an increasing avenue of HCV-related support.[51] In May, 2023, the Clinton Health Access Initiative and The Hepatitis Fund helped to facilitate price agreements with generic manufacturers (Viatris and Hetero) to provide sofosbuvir–daclatasvir to LMICs for US$60 per treatment course.[51,52] Increased funds and access to generics are promising steps towards HCV elimination. Continued monitoring of DAA uptake, preferably as part of national strategies, will be key to tracking progress towards WHO targets.[47,53]

Our work has limitations. In contrast to research conducted on DAA reimbursement in Canada and Europe,[14,17] there was often less written documentation available for countries in other regions and particularly for LMICs. Some countries, particularly LMICs, did not have online drug formularies, reimbursement forms, national plans, or clinical practice guidelines from which to extract data, or the existing data were from the interferon-based era. In addition, due to poor infrastructure or armed conflicts (or both), a few countries had unreliable internet access. Overall, countries had more information on HIV therapies, probably due to greater global financing, better data management systems, and in some cases, higher HIV burden.[54] Our data collection pertained to the DAA access of individuals aged 18 years and older. Research investigating DAA access for young people and children, who remain largely absent from national HCV plans and strategies, is merited.[20] The data collected in this Health Policy paper included DAAs that were subsidised, but costs might still be prohibitive for marginalised populations and people residing in LMICs.[23] Primary data collection occurred over 20 months, and the registration and reimbursement of DAAs might have changed in some countries within that period. However, our collaborator network was contacted in June and July, 2023, to rereview all presented data. Our findings cannot speak to the implementation of guidance documents among health-care practitioners (eg, a restriction could still be applied even if there is no written restriction in place) or how drug criminalisation laws[55,56] or other political, economic, and environmental factors affect DAA access. Our research did not report on all DAAs and might underestimate broader access. There were also circumstances in which a provider could technically apply to prescribe a DAA not listed in their country's regulatory agency, and our findings do not capture these circumstances. Additional research on other restrictions to reimbursed DAAs is warranted. This Health Policy paper focused on HCV treatment via public health-care systems. The role of private health-care systems in global and national HCV elimination strategies merits further enquiry.[48,57] Akin to other global reviews,[1] we could not retrieve information for all countries. Nonetheless, this Health Policy paper includes input from in-country experts representing nearly every included country, providing a critical resource and platform for future collaborations.

This Health Policy paper focused on HCV treatment. Investigating barriers to other pillars of the HCV care cascade will be essential to achieve WHO targets. WHO estimated that in 2019, only about 21% of people with HCV infection were diagnosed.[58] The newest testing technologies—eg, point-of-care HCV antibody and HCV RNA testing—remain out of reach in most countries due to high equipment costs, scarcity of trained personnel, and absence of country licensing agreements.[4,30,48,59,60] Some countries charge patients for viral load testing or genotype testing.[47,59] Using existing testing infrastructure—eg, for HIV or COVID-19—could increase the uptake of HCV testing.[57,61] Similarly, integrated HIV–HCV care has shown to be significantly associated with HCV treatment uptake and is often well received among patients, given an existing therapeutic relationship.[26,62,63] HCV self-testing (self-collection) might also broaden testing access and be cost-effective in some situations.[64]

This Health Policy paper provides new evidence regarding the registration and reimbursement of HCV therapies, including restrictions on reimbursement, permitting multicountry analyses and highlighting areas for growth. Although the list price of DAAs has become less prohibitive, cost is still a barrier for many countries.[30] Most countries had at least one pan-genotypic DAA registered, but reimbursement was suboptimal overall, particularly in LMICs. Among the reviewed restrictions, non-specialist prescribing is an especially key area for improvement. To meet WHO targets, efforts should be made to assist countries to increase access to DAA reimbursement and to ensure universal access by removing reimbursement restrictions.

Contributors

All authors contributed to the study design. All authors commented on a study concept sheet constructed by ADM and JG. All authors contributed to data collection. ADM, ARW, AK, NO, VP, and DJ conducted document searches. ADM, ARW, AK, and JG created the Global HCV and HIV Treatment Restrictions Group and collaborated with members. ADM, ARW, AK, EBC, AW, GJD, and JG contributed to data interpretation and data analysis. AW and EBC assisted with the production of tables and figures. ADM, ARW, AK, EBC,

and JG contributed to the drafting of the manuscript. ADM and JG wrote the original draft manuscript. All authors made substantial contributions to the editing and revising of the manuscript. All authors approved the final version of the manuscript and the decision to submit for publication.

Declaration of interests

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