
New recommendation on hepatitis C virus testing and treatment for people at ongoing risk of infection

Policy brief



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Background

In 2022, the World Health Organization (WHO) published the *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations*. These guidelines outline a public health response to HIV, viral hepatitis and sexually transmitted infections (STIs) for five key populations (men who have sex with men, sex workers, people in prisons and other closed settings, people who inject drugs and trans and gender diverse people).

In this policy brief, we give an update on those parts of the guidelines related to hepatitis C diagnosis and treatment for key populations.

Hepatitis C virus (HCV) contributes to disease burden and high mortality from chronic hepatitis C and its complications, such as cirrhosis and liver cancer, causing 290 000 deaths per year globally (1). Hepatitis C affects all WHO regions, but the burden is particularly high in the Eastern Mediterranean and European Regions. The 2022 Global Health Sector Strategy for viral hepatitis includes targets for 2030: to reduce the number of new HCV infections per year to 350 000 (down from a 2020 baseline of 1.575 million), and to reduce the number of new yearly HCV infections in people who inject drugs to 2 per 100 (down from a 2020 baseline of 8 per 100 people who inject drugs) (1).

HCV burden has been documented to be disproportionately high in people who inject drugs (2), people in prisons (3) and men who have sex with men, particularly in men who have sex with men living with HIV (4). Modelling shows that preventing, screening and treating HCV in key populations is needed to reach hepatitis C elimination goals (5-8).

The HCV response gained momentum during the Global Health Sector Strategy 2016–2021 implementation period. However, funding commitments remain inadequate to meet global goals. The number of people receiving treatment for chronic HCV infection increased almost tenfold from 2015, likely reducing hepatitis C-related mortality. Nevertheless nearly 80% of people living with HCV remain undiagnosed, and affordable treatments are not being accessed everywhere (1). There is inadequate coverage of harm reduction interventions (needle/syringe programmes (NSPs), opioid agonist maintenance therapy (OAMT) and community distribution of naloxone) for the prevention of viral hepatitis and HIV globally (9).

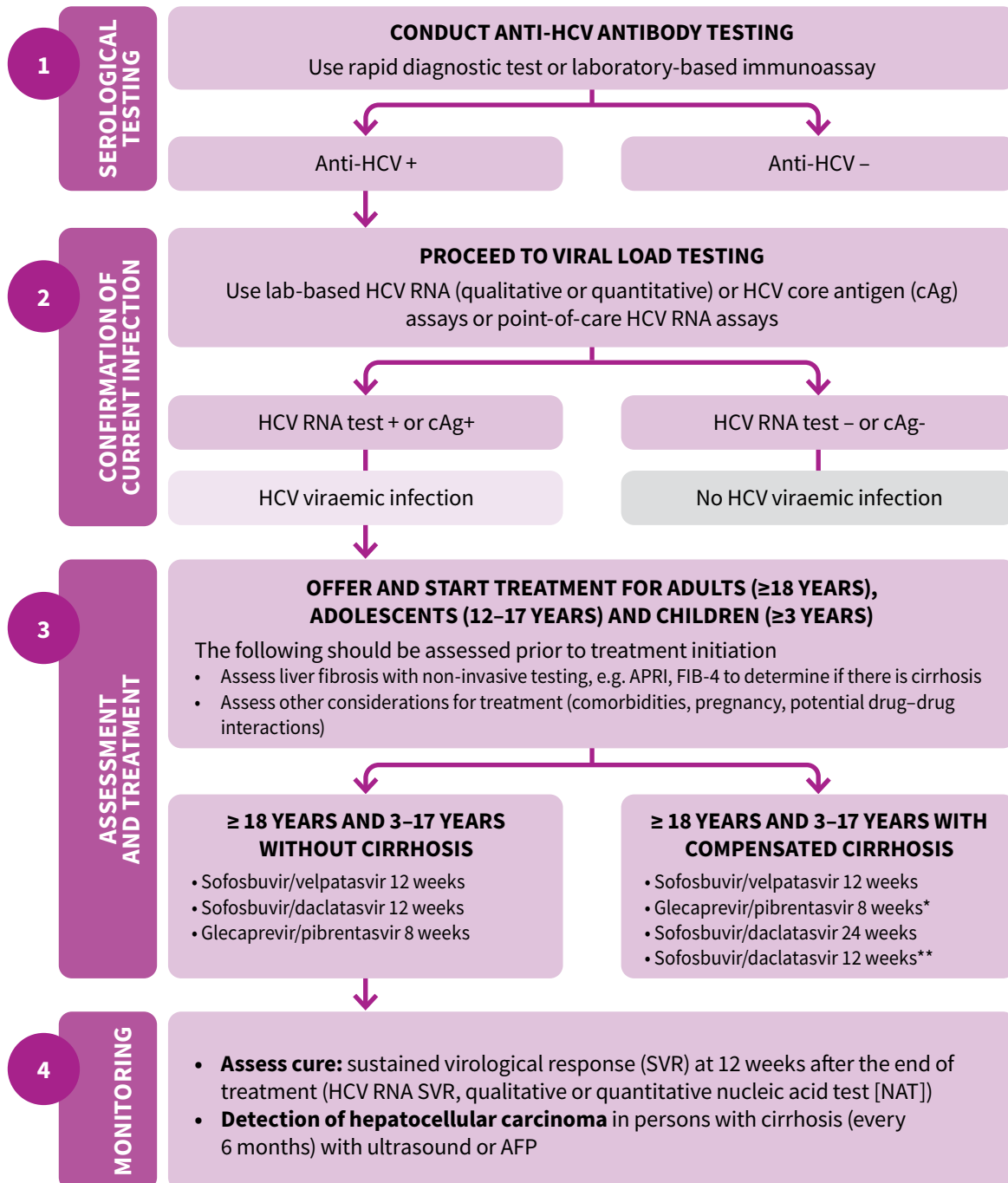
HCV can cause both acute (less commonly) and chronic disease. Recently acquired HCV infections are usually asymptomatic and rarely lead to symptomatic acute HCV. Following recently acquired HCV infection, approximately 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without treatment (5), with a median time to clearance of 16.5 weeks. Spontaneous clearance is more likely to occur in women, genotype 1 infection, and in people with clinical evidence of acute hepatitis, but is less likely to occur in people with HIV (10). The remaining 70% (55–85%) of persons will develop chronic HCV infection. Importantly, individuals that have cleared their HCV infection (spontaneously or through HCV treatment) are not immune to the virus, and those with ongoing risk and exposure can get reinfected.

Recognition of the benefits of treating and curing HCV infection for the reduction of onwards transmission is becoming a key part of a multifaceted public health approach to HCV elimination (6, 7). Early identification of HCV infection and reinfection is vital for a treatment-as-prevention approach, to reduce transmission, maintain reduced population prevalence and liver disease-related morbidity and mortality – especially in countries where many of the new HCV infections are among key populations.

WHO guidance for HCV testing, treatment and care

WHO recommends offering testing for HCV to all adults in settings where prevalence of HCV antibodies in the general population is over 2%, and focused testing in all settings for most affected populations, which usually includes the key populations listed above (11). To increase access and uptake of HCV testing, particularly among people from key populations, since 2021 WHO recommended HCV self-testing to be offered as additional approach to HCV testing services (12). WHO also recommends the treatment of all patients with chronic HCV infection, using pan-genotypic direct acting antivirals (13, 14) (Fig. 1). Additionally, since 2022 WHO recommends the decentralization and integration

Summary algorithm on HCV testing and treatment



* Persons who failed prior therapy with interferon, ribavirin, and/or sofosbuvir with HCV genotype 1, 2, 4–6 with cirrhosis should be treated for 12 weeks, and with HCV genotype 3 with or without cirrhosis should be treated for 16 weeks.

** May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.

of the delivery of HCV testing and treatment to peripheral health or community-based facilities, including primary care, harm reduction sites, prisons and HIV/ART clinics, as well as community-based organizations and outreach services (14). This set of recommendations is the backbone of an equitable, national, public-health focused HCV programme, and should be developed when building a national response to HCV.

In addition, WHO developed recommendations for retesting for presence of viremia after resolved infections and immediate treatment for those at ongoing risk. Both these recommendations have been developed in view of increasing patient choice, developing continuous engagement in care, and achieving and maintaining reduction of HCV transmission in vulnerable communities.

HCV retesting for presence of viremia after resolved HCV infection	
 NEW recommendation	People at ongoing risk and a history of treatment-induced or spontaneous clearance of HCV Infection may be offered 3-6 monthly testing for presence of HCV viremia (<i>conditional recommendation, very low certainty of evidence</i>). Remarks • Testing should be voluntary and not be used to further stigmatise any populations at ongoing risk. • Testing should be offered alongside primary prevention services that are evidence based and reduce transmission risks and in combination with appropriate treatment access and linkage. • To detect presence of viremic infection, the use of quantitative or qualitative nucleic acid testing (NAT) for detection of HCV RNA or alternatively an assay to detect HCV core antigen can be performed.

Several national and international guidelines, including WHO's, suggest serial testing for hepatitis C reinfection in priority groups, but do not state a specific testing frequency. A systematic review, commissioned by WHO, aimed to evaluate the current evidence regarding optimum testing frequency for HCV reinfection in priority groups after successful treatment or spontaneous clearance.

The review found very low certainty evidence, from one-armed observational studies and modelling studies (no eligible randomized control studies were found), in favour of more frequent retesting in people at ongoing high risk for HCV reinfection, particularly in people who inject drugs.

Pooled results from the 33 observational studies showed that among studies that reported a testing interval of 3–6 months, the pooled incidence estimate was higher than studies reporting testing less frequently than every 6 months. Additionally, among the people who inject drugs population, very low certainty evidence showed that pooled reinfection incidence was higher in those tested every 3–6 months compared to those tested less frequently than every 6 months.

Two additional modelling studies directly compared more and less frequent HCV testing regimes. The first modelled HCV reinfection in India found that ongoing annual testing was more effective, cost-saving and very cost-effective (15). The other model, among HIV-positive men who have sex with men, in France found that more frequent testing (3, 3–6 or 6-monthly) was associated with reductions in overall HCV incidence, as well as reductions in reinfection incidence (16).

These results indicate that more frequent testing may identify more infections, and could be beneficial in contributing to preventing onward transmission if individuals are linked to treatment and care. Patients may also benefit from better engagement in the *health care* system for other interventions, such as harm reduction.

While costs are very much dependent on setting, more frequent testing could involve increased short-term costs of tests, outpatient visits and, if more reinfections are identified, the short-term costs of increased treatment. However, long-term there may be cost savings by averting costs of advanced hepatitis and liver failure. This is supported by modelling evidence (15, 16).

Furthermore, short-term costs and accessibility of diagnostics for presence of viremia (nucleic acid amplification tests (NAAT) and HCV core antigen testing) may be a limitation to scaling up the recommendation in some settings.

HCV treatment for recently acquired infection in people



Pan-genotypic DAA-HCV treatment should be offered without delay to people with recently acquired HCV infection and ongoing risk (*strong recommendation, very low certainty of evidence*).

Remarks

- Individuals with recently acquired infection must have the option to make an informed choice about starting treatment immediately or delaying treatment initiation.
- Treatment for recently acquired infection should be offered alongside additional, evidence-based interventions to reduce HCV risk, and primary prevention services.

WHO currently recommends HCV therapy with pan-genotypic direct-acting antivirals (DAAs) for all persons with chronic infection over the age of 12 years and irrespective of disease stage. DAAs can cure most persons with chronic HCV infection, and treatment duration is short (usually 8 to 24 weeks), depending on the absence or presence of cirrhosis (13). However, DAA treatment is not currently approved by certain regulators for the treatment of recently-acquired hepatitis C (17). The rationale for this policy is to avoid unnecessary treatment and costs, since around 30% of people will clear the virus without treatment. More recently, clinical guidelines in Europe and the United States recommend the treatment of recently acquired infection, recognizing the benefits, such as reductions in loss to follow-up, avoiding chronic infection and reducing ongoing transmission (18, 19).

A systematic review was commissioned by WHO to determine the benefits and harms of immediate treatment of recently acquired HCV in people at ongoing risk, and to update the current body of evidence informing the timing of HCV treatment.

No randomized controlled trials nor comparative studies were identified in the systematic review. Twelve non-comparative studies were included. Three of these reported HCV incidence among men who have sex with men living with HIV and allowed a comparison of incidence before and after the implementation of an HCV treatment policy for recently acquired infection (20-22). Two of these studies reported a decrease in HCV incidence at the end of the study period (23, 24), but one found an increase in incidence over the study duration (21). These studies were in large cohorts of men who have sex with men, in which patients treated for recently acquired infections made up a minority of treated patients, while most patients were treated in the chronic phase of infection. As treating chronic hepatitis C can reduce incidence at population level (25) as well, it was not possible to identify the distinct effect of treating acute infection on incidence in these cohorts. Given the very low certainty, there is limited confidence in these results.

Cure rates when offering immediate or delayed treatment for people at ongoing risk are comparable. Seven studies that included a total of 567 participants with recently acquired hepatitis C reported sustained virological response at 12 weeks post-treatment (SVR12) in men who have sex with men, people living with HIV and people who inject drugs (26-32). The studies showed with a very low certainty evidence that people with ongoing risk treated for recently acquired HCV infection with DAA

achieved high rates of cure, consistent with the rates of cure seen for those treated with antivirals for chronic HCV in key risk groups. Evidence also showed that adherence and treatment completion among people at ongoing risk and given immediate HCV treatment was good (21, 23, 32-34).

Adverse events were reported in four studies (11, 32-34): one serious adverse event – an episode of rhabdomyolysis (rash and raised creatinine kinase) requiring hospitalization – was described (34), while all other adverse events were considered minor.

While evidence of effect was small across all outcomes, HCV treatment without delay for recently acquired HCV infection for those with ongoing risk can be beneficial at both the individual and population level. Improved identification and treatment of recently acquired HCV may bring benefits to the individual of being cured as soon as possible after diagnosis, rather than having to wait to access treatment and the associated risk of loss-to-follow-up, and thus would increase patient choices. There are potential broader population level benefits from curing individuals as soon as possible, namely, reducing the period of time during which they are infectious, thereby reducing HCV incidence in certain population networks and contributing to elimination of HCV. It is important to acknowledge, however, that following infection with hepatitis C, approximately one third of individuals will spontaneously clear the virus (i.e., cure without any medical intervention) (13). Treating all people with recently acquired HCV immediately means that people who would have otherwise cleared their infection spontaneously are unnecessarily exposed to the risk of adverse events, although, as stated previously, adverse events are very rare.

Modelling studies show that immediate DAA treatment is cost-effective and cost-saving compared to deferring treatment to the chronic stage (35-37).

Key population values and preferences

Multicountry, qualitative, key population values and preferences research was conducted to inform the development of the two HCV recommendations included in this policy brief. The results showed that awareness of and access to HCV treatment with pan-genotypic DAAs varied greatly across key populations, but those that were aware of treatment mostly reported ongoing barriers to the access and utilization of HCV services; these include cost, treatment delays, stigma and discrimination, and lack of research and political will. Several people who inject drugs noted that in certain contexts, cessation/abstinence from drug use (and sometimes even OAMT) continues to be used as a criteria for HCV treatment access, and in these circumstances can act as a major barrier to treatment.

Study participants recommended the expansion of HCV DAA treatment options and settings, including at NSPs, harm reduction services, OAMT clinics, drop-in centres and general health care settings, to maximize access and uptake. Participants further recommended that regular HCV RNA testing and retesting following cure should be made available and promoted similarly to HIV Test and Treat approaches, whereby regular monitoring is publicly and positively promoted, widespread testing is facilitated and immediate treatment for those diagnosed is encouraged.

Participants had an overwhelming preference for HCV services to be community-led and available within community settings in order to address concerns related to safety, confidentiality, stigma and discrimination, as well as criminalization.

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