ELIMINATING VIRAL HEPATITIS

Management of acute HCV infection in the era of direct-acting antiviral therapy

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Abstract | The management of acute HCV infection has not been standardized following the availability of direct-acting antiviral agents (DAAs) for chronic HCV infection, and substantial uncertainty exists regarding the optimal treatment regimen and duration. Despite the lack of direct evidence, the 2016 American Association for the Study of Liver Diseases (AASLD)–Infectious Diseases Society of America (IDSA) guidelines supported "the same regimens for acute HCV as recommended for chronic HCV infection … owing to high efficacy and safety", whereas the 2016 European Association for the Study of the Liver (EASL) guidelines recommended sofosbuvir–ledipasvir, sofosbuvir–velpatasvir or sofosbuvir plus daclatasvir for 8 weeks in acute HCV infection, with a longer duration of 12 weeks recommended for those infected with HIV and/or baseline HCV RNA levels >1,000,000 IU/ml. This Review outlines the epidemiology, natural history and diagnosis of acute HCV infection and provides contemporary information on DAAs for acute and recent HCV infection. The Review also discusses the 2016 AASLD–IDSA and EASL recommendations for acute HCV infection management in light of available evidence and highlights key differences in study populations and design that influence interpretation. We focus on populations at high risk of HCV transmission and acquisition, including people who inject drugs and HIV-positive men who have sex with men, and highlight the potential effects of diagnosis and treatment of acute HCV infection in contributing to HCV elimination.

Globally, an estimated 71 million people are living with chronic HCV infection, with ~2 million new infections occurring annually[1,2]. Key at-risk populations for HCV acquisition include people who inject drugs (PWID) and HIV-positive men who have sex with men (MSM)[3,4]. Unsafe health-care practices (including unsterile health-care injection) account for a large proportion of new HCV infections in low-income and middle-income countries[1,5].

One of the goals of the United Nations 2030 Agenda for Sustainable Development is the elimination of viral hepatitis as a public health threat, with targets including a 65% reduction in HCV-related mortality and an 80% reduction in HCV incidence[6,7]. To realize these elimination targets, strategies to improve HCV diagnosis, treatment and prevention will be required[8]. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence can be achieved by scale-up of targeted HCV treatment among those at highest risk of ongoing transmission, including PWID and HIV-positive MSM[9–12].

The development of direct-acting antiviral agents (DAAs; for example, grazoprevir–elbasvir[13], sofosbuvir–ledipasvir[14] and sofosbuvir–velpatasvir[15]) has revolutionized hepatitis C management and has provided the therapeutic tools required to strive for elimination[16,17]. With interferon-free DAAs established as the standard of care for chronic HCV infection, the optimal management of acute (duration of infection <6 months) and recent (duration of infection <12 months) HCV infection is uncertain. Much of the evidence regarding timing of treatment initiation, regimen choice and duration of therapy in recent HCV infection is based on small observational studies and randomized controlled trials of interferon-based therapy in selected populations. Administration of interferon-based therapy in recent HCV infection did offer a unique therapeutic advantage, with shorter treatment durations (4–12 weeks) and higher efficacy (SVR 72–87%)[18–22] in comparison with the same treatment in chronic HCV infection (duration 24–48 weeks, SVR < 60%)[23,24]. The efficacy and optimal duration of DAAs in recent HCV infection are being evaluated.

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Key points

- In 2015, an estimated 1.75 million new HCV infections occurred worldwide, with injection drug use and unsafe health-care practices being the predominant modes of transmission.
- Access to HCV care, education and treatment for people at high risk of onward transmission, including those with acute and recent HCV infection, should be a priority.
- Monitoring HCV RNA levels for between 4 and 12 weeks following diagnosis of acute infection provides an opportunity to assess for spontaneous clearance without compromising outcome.
- The role of (ultra-)short duration direct-acting antiviral agents in recent HCV infection is under investigation; pending the results of large trials, treatment is recommended with the same regimens as for chronic HCV infection.
- Screening of at-risk populations (at least annually) is recommended to improve diagnosis and treatment of acute HCV infection.
- Early detection and re-treatment of HCV reinfection, along with education and harm reduction, should be incorporated into the individual-level and population-level HCV response.

This Review outlines the epidemiology, natural history and diagnosis of acute HCV infection and provides contemporary information on DAAs for recent HCV infection. The Review also discusses the 2016 American Association for the Study of Liver Diseases (AASLD)–Infectious Diseases Society of America (IDSA) and European Association for the Study of the Liver (EASL) recommendations for acute HCV management in light of available evidence and highlights key differences in study populations and design that influence interpretation and clinical utility. In this Review, we focus on populations at high risk of HCV transmission and acquisition, including PWID and HIV-positive MSM, and highlight the potential influence of diagnosis and treatment of recent HCV infection in contributing to HCV elimination.

HCV incidence and transmission

In 2015, an estimated 1.75 million new HCV infections occurred worldwide (global incidence: 23.7 per 100,000)[1,2]. Although the HCV incidence seems to have decreased in the twenty-first century compared with that in the second half of the twentieth century (reviewed elsewhere[25]) in most jurisdictions, substantial regional variation exists, with continuing high HCV infection incidence in Europe (61.8 per 100,000) and the eastern Mediterranean region (62.5 per 100,000)[1]. Country-specific data demonstrated that the annual HCV incidence peaked in the vast majority of countries between 1970 and 2005; the exception, with increasing HCV incidence, is Russia[26,27]. Although unsafe health-care procedures account for much of the HCV transmission in the eastern Mediterranean region[28], injecting drug use predominates in Europe, particularly in eastern Europe[1,29,30].

People who inject drugs. Of the estimated 1.75 million new HCV infections in 2015, 23% were attributable to current injecting drug use[1] (with an estimated number of PWID aged 15–64 years in 2015 of 15.6 million and an anti-HCV antibody prevalence among PWID of 53%[31]). The majority of new (60%) and existing (80%) HCV infections in developed countries occurs among PWID[3,32], with higher incidence in specific populations, including young adults (aged <30 years)[33–38] and those who are incarcerated[39–42]. HCV acquisition risk is greatest among young adults who inject drugs in the first years of unsafe injection practices[43,44].

Although stable or declining HCV incidence among PWID has been reported in some jurisdictions (including western Europe and Australia)[45,46], sustained high or increasing incidence has been reported in other regions, including the developing world and the United States[37,47–49]. Data compiled by the US Centers for Disease Control and Prevention demonstrated that whereas HCV incidence remained fairly constant in all age groups between 2002 and 2014, an increase in incidence was noted between 2010 and 2014 in people aged 20–29 years (2010: 0.75 per 100,000; 2014: 2.20 per 100,000) and people aged 30–39 years (2010: 0.60 per 100,000; 2014: 1.66 per 100,000)[48]. This increase coincided with HCV (and HIV) infection outbreaks among PWID in non-urban communities and was frequently associated with misuse of prescription opiates before use of heroin[37,47,50]. Other demographic and clinical factors associated with HCV seroconversion include sharing injecting and drug preparation equipment, high injecting frequency, high number of injecting partners, type of drug injected, pooling money to purchase drugs, unstable housing and HIV co-infection[43,45,51–54]. Young female PWID are at greater risk of HCV acquisition than men[55,56], which is potentially related to high-risk injecting behaviours in the setting of coexisting sexual and injecting relationships[55,57].

Access to health services and implementation of evidence-based harm reduction programmes are necessary to reduce the burden of HCV among PWID, with reduced HCV incidence seen among PWID receiving opioid substitution therapy (OST)[36,45,53,58–62]. Furthermore, the combination of OST and high-coverage needle and syringe programmes (ensuring adequate needles or syringes to cover all injecting episodes) can reduce HCV incidence by up to 80%[52,59,63–67].

People with HIV infection. Increasing HCV infection incidence and prevalence have been reported in large cohorts of HIV-positive MSM over the past decade[4,68–78], although the overall burden of disease remains markedly lower than that among PWID (with an estimated number of people living with HIV–HCV co-infection of 2.3 million (including 1.4 million PWID) and an anti-HCV antibody prevalence among people with HIV infection of 6.2% (MSM 6.4% and PWID 82.4%)[79]). A meta-analysis examining HCV infection incidence in HIV-positive MSM who denied ever injecting drugs reported an increase in annual incidence from 0.4 per 100 person-years in 1991 to 1.3 per 100 person-years in 2012 (REF.[68]). However, differences in study design have resulted in high variability in incidence estimates between cohorts, with HCV infection incidence stabilizing or decreasing in some jurisdictions[11,80]. Given the changes to international guidelines promoting enhanced HCV screening among HIV-positive MSM, HCV testing, diagnosis and prevalence have increased in many

Box 1 | **Case definitions for acute HCV infection**

Anti-HCV antibody seroconversion
The most accurate case definition of acute HCV infection is detection of HCV RNA levels in an individual with documented anti-HCV antibody seroconversion (with test conversion within 12 months)[32,102–105].

Acute clinical HCV infection
An acute clinical illness with symptoms and signs consistent with acute viral hepatitis, including jaundice and/or elevated alanine aminotransferase (ALT) >5–10 times the upper limit of normal, with corresponding laboratory diagnostic evidence (positive anti-HCV antibody and/or detectable HCV RNA)[32,102–105,130].

HCV RNA detected, anti-HCV antibody negative
Detection of HCV RNA with a negative anti-HCV antibody result, followed by seroconversion, suggests very recent infection with exposure in the previous 6–8 weeks[32,103].

European countries, whereas incidence has plateaued or decreased in these same countries[11,78,80].

The reported increase in HCV infection incidence in HIV-positive MSM has been associated with an increase in sexual risk behaviour and recreational drug use[68]. Permucosal (sexual) HCV exposure (with blood as the medium) seems to facilitate HCV transmission, with risk factors for HCV acquisition including condomless traumatic anal intercourse, higher number of sexual partners, group sex, ulcerative sexually transmitted diseases and sexual acts that involve trauma and bleeding[68,69,73,74,81–83]. The increase in HCV infection incidence has occurred in parallel with certain behavioural trends in MSM communities, including use of social media sexual networking applications, 'serosorting' sexual behaviours (use of HIV serostatus in decision-making regarding sexual behaviour) and the phenomenon of 'chemsex' (illicit drug use, largely methamphetamine, before or during sex by both injecting and non-injecting routes of administration)[83–88], highlighting that HIV-positive MSM and PWID are not mutually exclusive. HIV-positive MSM who inject drugs are at higher risk of HCV acquisition than HIV-positive MSM who do not inject drugs[72]. However, HIV-positive MSM who report injecting drug use could exhibit different drug use and sexual behaviours than non-MSM PWID populations traditionally reported in the HCV literature, and as such, different management and prevention strategies might need to be used.

Although similar sexual risk behaviours have been reported in HIV-positive and HIV-negative MSM, HCV infection incidence seems to be markedly lower in HIV-negative MSM[89–92]. However, with increasing use of HIV pre-exposure prophylaxis (PrEP), there is the potential for a reduction in serosorting of sexual partners and increased sexual risk behaviour and transmission of HCV among HIV-positive and HIV-negative MSM populations[83,88,93,94]. Incident HCV infections have been observed in HIV-negative MSM receiving HIV PrEP[92,94–96]. Phylogenetic analysis of NS5B sequences obtained from HCV-positive HIV-negative MSM receiving PrEP in Amsterdam (the Netherlands) suggests that HCV transmission is occurring within discrete populations, with MSM-specific HCV clusters containing both HIV-positive and HIV-negative individuals[88]. Although current guidelines do not support routine HCV screening of HIV-negative MSM, the increasing use of HIV PrEP and overlapping behavioural networks support the monitoring of HCV incidence among high-risk MSM to guide policy.

Health-care-associated HCV transmission. Unsafe health-care procedures (including unsafe health-care injection, blood transfusion and other invasive medical procedures) continue to account for a substantial proportion of new HCV infections (15–20% per year), largely in developing countries[28,97,98]. In 2010, an estimated 5% of all health-care injections were given with unsterilized, reused equipment, resulting in an estimated 315,000 new HCV infections, most of which were in the eastern Mediterranean and southeast Asia[98]. Coupled with poor injection practices, excessive medication administration by injection contributes to transmission[5,97]. In these regions, training of health-care providers, structural changes to health-care models, effective screening and investment in HCV diagnostics, disposable materials (ideally with reuse-prevention devices) and effective sterilization procedures will be required to reduce health-care-associated HCV transmission[5].

Following the broad implementation of universal infection control procedures, there have been marked declines in HCV incidence among haemodialysis populations in high-income countries[99,100], a group previously at high risk of HCV acquisition. However, transmission outbreaks in dialysis units still occur[101], screening is recommended in these patients[102] and high HCV infection incidence and prevalence among dialysis-recipients in developing countries[99] remain a concern.

Diagnosis of acute HCV infection

Difficulties in diagnosis. Acute HCV infection refers to the 6-month period following infection acquisition, though case definitions vary[102–105] (BOX 1). Establishing the diagnosis of acute HCV infection can be challenging. Clinical features suggestive of acute HCV infection include marked elevation of alanine aminotransferase (ALT) levels (>5–10 times the upper limit of normal) and an acute illness manifested by jaundice, fever, headache, malaise, anorexia, nausea, vomiting, diarrhoea or abdominal pain[32,106]. However, only 15–30% of those infected with HCV develop a symptomatic illness[106], and ALT level elevation is nonspecific.

Anti-HCV antibody seroconversion provides the most accurate case definition, but the window between exposure and seroconversion is variable. Anti-HCV antibodies are usually detectable within 6–12 weeks of exposure[107] but can take up to 12 months in immunocompromised individuals[108–110] or might not occur at all (<5% of those exposed)[110], necessitating assessment with HCV RNA levels as part of the initial evaluation in this population. Furthermore, individuals who have cleared previous HCV infection will remain indefinitely anti-HCV antibody positive[32,111], and as such, HCV RNA level is required to diagnose reinfection.

No definitive laboratory test exists to distinguish acute from chronic HCV infection. Certain features can be suggestive of acute infection, including low ($<10^4$ international units (IU)/ml) or fluctuating (>1 $\log_{10}$ IU/ml) serum HCV RNA titre[112,113]. Although the use of HCV core antigen testing is supported for diagnosis of acute HCV infection[105], test performance (largely sensitivity) and subsequent clinical utility are affected by the potential for low-level viraemia in acute infection, with the lower limit of HCV core antigen detection equivalent to 500–3,000 HCV RNA IU/ml depending on HCV genotype[114,115].

Point-of-care tests for HCV infection, particularly for HCV RNA, have the potential to simplify diagnostic and screening algorithms, increase acute HCV infection diagnoses and facilitate early linkage to care and treatment. Point-of-care HCV testing can include oral fluid rapid diagnostic testing[116–120], finger-stick whole blood rapid diagnostic testing[117–122], on-site venepuncture-based testing[123,124] and finger-stick capillary whole blood testing[125,126]. Although most of these tests detect anti-HCV antibody, point-of-care HCV RNA assays that are available or in late-stage development include the Xpert HCV Viral Load (Cepheid) test, HCV ID Kit (Genedrive) and Truenat HCV (Molbio). Validation of these tests in the setting of recent HCV infection is ongoing.

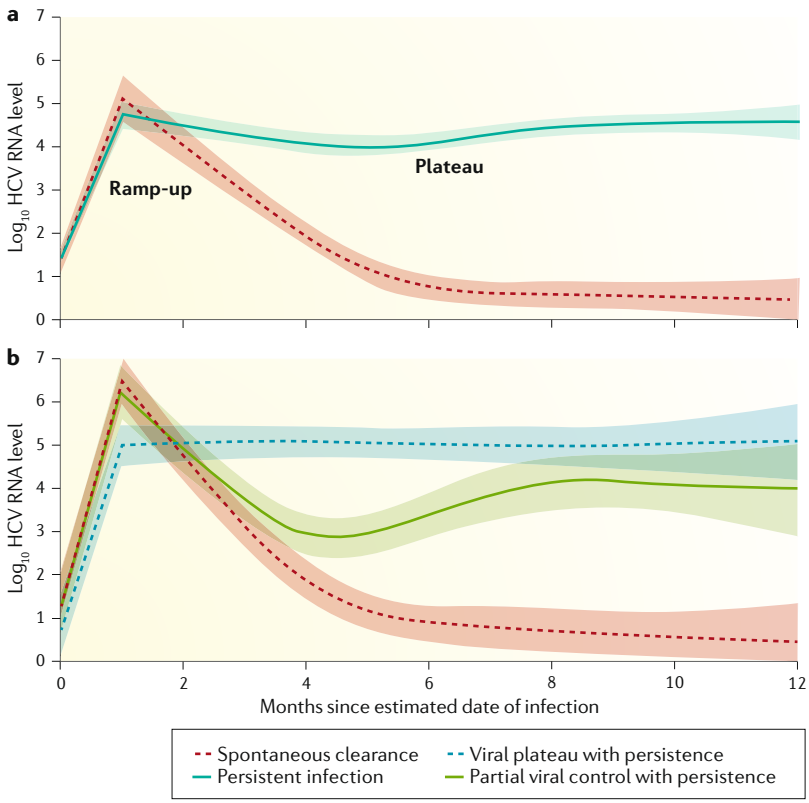

Fig. 1 | **Viral kinetics in acute HCV infection. a** | Acute HCV infection results in either spontaneous clearance (red) or viral persistence (blue green) and chronic HCV infection. Three phases have been described between exposure and seroconversion: the 'pre-ramp-up' phase (2–14 days) with intermittent low-level viraemia, potentially below the level of detection (not shown), the 'ramp-up' phase (8–10 days) with an exponential rise in HCV RNA and the 'plateau' phase (45–68 days) in which HCV RNA stabilizes. **b** | Divergence in HCV RNA dynamics in individuals who demonstrate spontaneous clearance and in those who have viral persistence occurs at approximately 3 months following infection. Among individuals with viral persistence, two HCV RNA patterns are noted — viral plateau with persistence (blue) and partial viral control with persistence (green). Among individuals with partial viral control and persistence, an initial marked decline in HCV RNA (potentially below the level of quantification) is followed by viral rebound, representing viral escape from innate responses or a failure of HCV-specific adaptive responses. Adapted from REF.[113], CC BY 4.0.

Screening strategies in high-risk populations. Different screening strategies for HCV infection have been recommended and implemented depending on regional epidemiology[102,105,127,128]. As documentation of seroconversion is often difficult, routine monitoring of at-risk populations is recommended to improve diagnosis of acute HCV infection. All PWID should be screened for HCV with anti-HCV antibody, and in the setting of ongoing injecting drug use, screening every 6–12 months should be performed to assess for incident infection[102,105,129]. Similarly, all newly diagnosed HIV-positive individuals should be screened for HCV antibody[102,130]. HIV-positive MSM at risk of HCV acquisition should be reviewed every 6–12 months with assessments for ALT levels and anti-HCV antibody[130]. After potential exposure (via injecting drug use and/or high-risk sexual behaviour) or diagnosis of a sexually transmitted infection in MSM, additional HCV screening with anti-HCV antibody should be considered and repeated 3 months later if negative[130]. HCV RNA assays should be performed if transaminases (particularly ALT) are elevated or if HCV reinfection is suspected[131]. If these recommendations are adhered to, both HCV primary infection and reinfection should be identified within the first year of acquisition. As such, a broader definition of recent HCV infection (duration of infection <12 months) has greater utility in guiding policy and management decisions.

Management of recent HCV infection

Natural history and spontaneous clearance. The natural history of recent HCV infection must be taken into consideration when determining the optimal management strategy. The complex interplay between host and virus in acute infection results in either viral persistence (75–85%) or spontaneous clearance (15–25%)[132–136], with divergence in HCV RNA dynamics between the two groups occurring at approximately 3 months after infection[113] (FIG. 1). In most cases, spontaneous clearance occurs in the first 6 months (67–86%) or 12 months (83–95%) following HCV acquisition[137–140]. Both host[113,132,134,136,139,141–146] and viral[113,136,147,148] factors have been associated with spontaneous clearance, although the evidence for and importance of host factors is most robust (BOX 2). Single-nucleotide polymorphisms in the *IFNL3* and *IFNL4* genes (formerly *IL28B*) have been identified that strongly predict both spontaneous clearance and clearance in response to interferon-based therapy[136]. Broad and multi-specific $CD4^+$ and $CD8^+$ T cell responses are associated with spontaneous clearance, whereas the failure of a sustained T cell response of sufficient magnitude is associated with viral persistence[142,143]. Unsurprisingly, immunocompromised hosts have a reduced chance of spontaneous

Box 2 | **Factors associated with spontaneous clearance of HCV infection**

Host factors

- Female sex[132,136,139,218,219]
- Younger age[220]
- White ethnicity[221]
- Symptomatic (icteric) acute hepatitis[218,222]
- Absence of HIV or HBV co-infection[221]
- *IFNL3* and/or *IFNL4* genotype (single nucleotide polymorphism rs12979860; CC versus CT or TT)[136,222–224]
- HLA class II alleles DQB1*02, DQB1*03, DRB1*04 and DRB1*11 (REF.[144])
- HCV-specific T cell response[142,143]

Viral factors

- HCV genotype 1 (REFS[136,141,225])
- High peak HCV RNA level[226,227]
- Reduced diversity of HCV quasispecies[148]

clearance (≤20%)[110,133,141,149–153]. Despite extensive study of the innate and adaptive immune responses in acute and chronic HCV infection, the specific immunological characteristics during the acute phase of infection that predict clearance remain incompletely understood (reviewed elsewhere[154,155]).

Timing of HCV treatment initiation. The potential for spontaneous clearance needs to be weighed against early treatment initiation. Clinical trial data examining the utility of interferon-based therapy suggested that observation for 12 weeks following diagnosis of acute HCV infection provided an opportunity to assess for spontaneous clearance without compromising treatment efficacy, whereas a more prolonged delay (>12 weeks) risked losing individuals to follow-up[156,157]. Additionally, monitoring HCV RNA kinetics in the first 4–12 weeks after diagnosis could assist in optimizing early treatment initiation[112,137]. For instance, among HIV-positive MSM, a decline in HCV RNA levels of ≥2 $\log_{10}$ IU/ml at week 4 after diagnosis was associated with spontaneous clearance, whereas detectable HCV RNA at week 12 after diagnosis was associated with persistence[130,158,159]. Subsequent demonstration of the clinical utility of viral kinetic monitoring in the 4 weeks following diagnosis followed by early treatment (if spontaneous clearance is deemed unlikely) has influenced acute HCV treatment recommendations in this population[130,159,160].

There is no role for pre-exposure or post-exposure prophylaxis in HCV infection[102,105]. The natural history of HCV infection, efficacy of DAAs and cost-effectiveness modelling do not support pre-emptive therapy[161]. Instead, appropriate testing and expedient treatment, if required, are recommended.

DAAs for acute and recent HCV infection. The treatment paradigm for chronic HCV infection has evolved rapidly, with dual-class and triple-class DAA regimens for 8–12 weeks achieving very high SVR (>95%) in treatment-naive individuals without cirrhosis[16,17]. Although this DAA approach has markedly reduced the relevance of enhanced interferon-based treatment outcomes in acute HCV infection, the potential for shortened duration therapy in acute and recent HCV infection underpins current treatment recommendations and research questions. Compared with chronic HCV infection (treatment duration 24–48 weeks, SVR at 24 weeks (SVR24) <60%)[23,24], clinical trials of shortened duration (4–12 weeks) PEG-IFN with and without ribavirin demonstrated superior efficacy in acute and recent HCV infection (SVR24 72–87%)[18–22], with similar efficacy in populations with acute (<6 months)[19,20,157,162–166] and early chronic (6–24 months) infection[22,166].

The optimal management of acute HCV infection in the era of DAAs is yet to be defined. The 2016 AASLD–IDSA guidelines support "the same [direct-acting antiviral] regimens for acute HCV as recommended for chronic HCV infection … owing to high efficacy and safety" (level of evidence: class IIa, level C), whereas the 2016 EASL guidelines recommend sofosbuvir plus a non-structural protein 5A (NS5A) inhibitor (sofosbuvir–ledipasvir, sofosbuvir–velpatasvir or sofosbuvir plus daclatasvir) for 8 weeks in acute HCV infection (level of evidence: class IIb, level C), with a longer duration of 12 weeks recommended for those with HIV and/or baseline HCV RNA >1,000,000 (>6 $\log_{10}$) IU/ml (level of evidence: class IIb, level C). Current international recommendations for the treatment of acute HCV infection are controversial, are not supported by robust evidence and will evolve pending the results of current and future clinical trials. Several small clinical trials and cohort studies of shortened duration DAA therapy have been conducted (TABLE 1; Supplementary Table 1), and larger trials are underway (TABLE 2) to fill this evidence gap. Pilot studies of a single DAA, sofosbuvir, with ribavirin showed suboptimal efficacy in acute and recent HCV infection and are not recommended[167,168].

Shortened duration dual-class and triple-class DAA regimens for 4, 6 and 8 weeks have demonstrated promising results (FIG. 2). In acute HCV genotype 1 mono-infection, very high SVR was demonstrated with 6 weeks of sofosbuvir–ledipasvir (26 of 26 patients; SVR at 12 weeks (SVR12) intention to treat (ITT) 100%)[169]. Notably, PWID were excluded, and the vast majority of study participants had symptomatic infection and low baseline HCV RNA levels (median 4.0 $\log_{10}$ IU/ml; ≤3 $\log_{10}$ IU/ml, 45%). Again, in a preliminary report in acute HCV genotype 1 mono-infection, high SVR was demonstrated with 4 weeks of sofosbuvir–ledipasvir (14 of 14 patients; SVR12 ITT 100%) and 8 weeks of sofosbuvir plus simeprevir (13 of 15 patients; SVR12 ITT 87%)[170]. Viral suppression was rapid, with HCV RNA levels below the limit of detection in 93% at week 1 among participants who received either sofosbuvir–ledipasvir or sofosbuvir plus simeprevir. Current PWID were excluded. This study is yet to be formally published, and as such, without a fuller description of the study design, definitions and methodology, no firm conclusions can be drawn. Among HIV-positive MSM, lower SVR (20 of 26 patients; SVR12 ITT 77%; per-protocol 87%) was demonstrated with 6 weeks of sofosbuvir–ledipasvir for acute HCV genotypes 1a and 4 (REF.[171]). The mean baseline HCV RNA level was 5.4 $\log_{10}$ IU/ml. The majority of study participants were asymptomatic; two participants presented with jaundice, and both were

Table 1 | **Interferon-free direct-acting antiviral agent clinical trials in acute and recent HCV infection**

Study setup (year; country; design)	Protocol-defined duration of infection at screening (months)	Duration of infection at baseline (weeks), median (range)	PWID (%)	HIV (%)	HCV genotype	Baseline HCV RNA level (log_{10} IU/ml), median (range)	Baseline HCV RNA >1,000,000 IU/ml, *n* (%)	Regimen, duration (weeks)	SVR12 (ITT)
Clinical trials									
2016 (REF.[167]); Australia and New Zealand; multicentre	≤12	37 (12–55)	84	74	• 1a: 68% • 2b: 5% • 3: 26%	5.4 (1.5–7.4)	8 (42)	SOF + RBV (6)	32% (6/19)
2017 (REF.[168]); USA; multicentre	≤6	20[a] (13–25)	24	100	• 1a: 65% • 1b: 12% • 1: 12% • 2b: 6%	6.4 (5.4–6.6)[b]	11 (65)	SOF + RBV (12)	59% (10/17)
2016 (REF.[170]); Germany; multicentre	≤4	U	0	0	• 1a: 55% • 1b: 45%	4.0 (1.2–7.2)	2 (10)	SOF–LDV (6)	100% (20/20)
2017 (REF.[175]); Germany and UK; multicentre	≤6	U	U	100	• 1a: 73% • 4: 27%	5.4[c] (1.1–7.3)	10 (38)	SOF–LDV (6)	77% (20/26)
2017 (REF.[172]); Australia, England and New Zealand; multicentre	≤12	30 (11–51)	53	77	• 1a: 93% • 1b: 3% • 1 or no subtype: 3%	5.7 (2.7–7.3)	13 (43)	PrOD ± RBV (8)	97% (29/30)
2017 (REF.[171]) (abstract only); USA; multicentre	≤6	U	19	100	• 1: 96% • 4: 4%	6.2 (4.5–6.6)[b]	NA	SOF–LDV (8)	100% (27/27)
Cohort studies									
2015 (REF.[170]) (abstract only); USA; multicentre	Not defined	U	100	0	• 1a: 50% • 1b: 50%	6.1[d]	U	SOF–LDV (4)	100% (14/14)
		U	100	0	• 1a: 47% • 1b: 53%	6.2[d]	U	SOF + SIM (8)	93% (13/15)
2017 (REF.[231]); USA; single centre	Not defined	22[e] (4–38)	37	100	• 1a: 83% • 1b: 17%	4.5 (1.7–7.5)	4 (33)	SOF + RBV (12)	92% (11/12)

ITT, intention to treat; IU, international units; LDV, ledipasvir; MSM, men who have sex with men; NA, not available; PrOD, paritaprevir–ritonavir–ombitasvir + dasabuvir; PWID, people who inject drugs; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR12, SVR at 12 weeks; U, unknown. [a]Time from first laboratory evidence of acute HCV infection until study entry. [b]Median (interquartile range). [c]Mean (range). [d]Mean HCV RNA level. [e]Time from diagnosis to treatment commencement.

receiving atazanavir. Of the six participants who did not achieve SVR12, three experienced post-treatment relapse, one was reinfected before post-treatment week 4, and two were lost to follow-up after achieving SVR4. The three participants with relapse had high baseline HCV RNA levels (>6.9 log_{10} IU/ml). Among people with acute and recent HCV genotype 1, excellent efficacy has been reported with 8 weeks of paritaprevir–ritonavir–ombitasvir and dasabuvir[172] (29 of 30 patients; SVR12 ITT 97%; per-protocol 100%) and in a preliminary report with 8 weeks of sofosbuvir–ledipasvir[171] (27 of 27 patients; SVR12 ITT 100%). Combined, these pilot studies offer exciting potential but are limited by small sample sizes, selected populations and, in some cases, lack of formal published results.

Marked differences in study design and cohort characteristics limit meaningful comparison and generalization with published guidelines (TABLE 2; Supplementary Table 1). Most of the study populations have been highly selected, often delineated by HIV serostatus. Unfortunately, current PWID have largely been excluded[169,170,173], a population in which targeted screening and treatment of acute HCV infection could be most useful to prevent ongoing transmission. Additionally, different or unclear definitions of duration of infection make comparison and implementation uncertain. As the distinction between acute and early chronic infection is somewhat arbitrary, further research regarding treatment initiation within 1 year of infection would permit broad clinical application.

Predictors of response to shortened duration DAA therapy in acute HCV infection. Baseline HCV RNA level and early on-treatment viral kinetics seem to influence response to short duration DAA therapy (treatment duration ≤6 weeks)[174]. A higher baseline HCV RNA level (>6 log_{10} IU/ml) seems to be associated with post-treatment relapse following short duration therapy in acute[167,175] and chronic[176] HCV infection. In preliminary results from two acute HCV infection clinical trials examining an 8-week duration of sofosbuvir–ledipasvir[171] and paritaprevir–ritonavir–ombitasvir and dasabuvir[172], baseline HCV RNA level did not affect efficacy.

Given the potential for high, fluctuating HCV RNA levels in recent HCV infection[113], an ultra-short duration therapeutic strategy might require stratification by baseline HCV RNA titres. There is precedent for this approach in chronic HCV infection, with post hoc analysis of the ION-3 trial forming the basis for prescribing guidelines regarding shortening the treatment duration of sofosbuvir–ledipasvir from 12 weeks to 8 weeks in treatment-naive individuals who have chronic

Table 2 | **Registered interferon-free direct-acting antiviral agent clinical trials in acute and recent HCV infection**

Principal investigator	Country; year registered or commenced	Short title (ClinicalTrial.gov number)	Duration of infection (months)	Study population	*n*	Regimen	Treatment duration (weeks)	Status
Naggie	USA; 2014	SWIFT-C (NCT02128217)	≤6	GT 1 (HIV-positive and PWID eligible)	27	SOF–LDV	8	Closed to recruitment; SVR12 27/27
Matthews and Nelson	Australia, New Zealand and UK; 2016	TARGET3D (NCT02634008)	≤12	GT 1 (HIV-positive and PWID eligible)	30	PrOD (±RBV)	8	Closed to recruitment; SVR12 29/30
				GT 1–6 (HIV-positive and PWID eligible)	30	G–P	6	Recruiting
				GT 1–6 (HIV-positive and PWID eligible)	30	G–P	4	Not yet recruiting
Rijnders	Netherlands and Belgium; 2016	DAHHS-2 (NCT02600325)	≤6	GT 1 or 4 (HIV-positive and PWID eligible)	80	GZR–EBR	8	Closed to recruitment
Matthews	International; 2016	REACT (NCT02625909)	≤12	GT 1–6 (HIV-positive and PWID eligible)	250	SOF–VEL	6 or 12 (RCT 1:1)	Recruiting
Lacombe	France; 2016	SAHIV (NCT02886624)	≤6	GT 1 or 4 (HIV-positive and PWID eligible)	50	GZR–EBR	8	Not yet recruiting

EBR, elbasvir; G–P, glecaprevir–pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; PrOD, paritaprevir–ritonavir–ombitasvir plus dasabuvir; PWID, people who inject drugs; RBV, ribavirin; RCT, randomized controlled trial; SOF, sofosbuvir; SVR12, SVR at 12 weeks; VEL, velpatasvir.

HCV genotype 1 infection and baseline HCV RNA levels <6,000,000 IU/ml but do not have cirrhosis[14,177,178]. Among treatment-naive individuals in China with chronic HCV genotype 1b infection and without cirrhosis ($n = 18$), a pilot study evaluated ultra-short duration response-guided triple-class DAA therapy[179]. Very high SVR (100%) was seen among those who received 3 weeks of DAAs after achieving an ultra-rapid viral response (defined as HCV RNA titre <500 IU/ml after 48 h). Participants with an ultra-rapid viral response had a significantly lower mean baseline HCV RNA level than those without an ultra-rapid viral response (HCV RNA 6.0 $\log_{10}$ IU/ml (s.d. 0.8) versus 7.0 $\log_{10}$ IU/ml (s.d. 0.3); $P < 0.001$), suggesting that baseline HCV RNA levels can assist in predicting which individuals might respond favourably to short duration therapy, although the findings need confirmation in other populations (such as in different ethnicities or in patients infected with different genotypes). Although the 2016 EASL guidelines support stratification of treatment duration by HIV serostatus and baseline HCV RNA levels[105], the evidence for this recommendation is very limited.

Future research directions. The role, efficacy and cost-effectiveness of interferon-free DAA therapy in the management of recent HCV infection require further evaluation. It is uncertain whether the paradigm of shortened treatment duration in recent, as compared with chronic, HCV infection will hold true with interferon-free therapy. Although the data from small studies support this concept (TABLE 1), the results of larger (randomized) clinical trials are awaited to confirm these findings (TABLE 2). To robustly evaluate the efficacy of ultra-short duration DAA therapy, optimal regimen choice will be critical. Mathematical modelling suggests that rapid on-treatment second-phase viral decline, as seen after administration of HCV non-structural protein 3 (NS3) and/or non-structural protein 4 A (NS4A) protease inhibitors and NS5A inhibitors, permits shorter (potentially by weeks) treatment durations[180,181]. Additional modelling suggests that analysis of early on-treatment viral kinetics reduces DAA treatment duration, with individualized (response-guided) therapy associated with a projected average cost saving of 16–20% per 100 patients with chronic HCV infection treated[174]. However, treatment individualization increases complexity and limits utility. Cost-effectiveness analysis supports the immediate treatment of acute HCV infection with short duration DAAs (4–6 weeks) as compared with treatment deferral until chronic infection (treatment duration 8–12 weeks), as there are cost savings associated with shorter duration and reduced transmission[182].

The effect of clinical, virological and immunological factors on efficacy, as measured by factors such as HIV infection, baseline HCV RNA levels, clinical presentation and duration of infection, remains to be adequately determined. Although administration of interferon in acute HCV infection seemed to have a unique role in improving response to therapy owing to differences in expression of interferon-stimulated genes[183], the effect of host genetics and immune response on treatment outcome with DAAs in recent HCV infection is unknown.

Studies to date have been largely restricted to acute HCV genotype 1 infection[169,175]. A pan-genotypic strategy would be ideal for clinical implementation and might permit a simplified management strategy in which assessment of HCV genotype is no longer required and a single short duration DAA regimen would be suitable for most people with acute and recent HCV infection. The FDA approval of glecaprevir–pibrentasvir in August 2017 (REF.[184]), an 8-week pan-genotypic regimen for people with chronic HCV infection without cirrhosis (fibrosis stage 0–3), suggests that such an approach is possible for the vast majority of people infected with HCV regardless of duration of infection. Large studies of

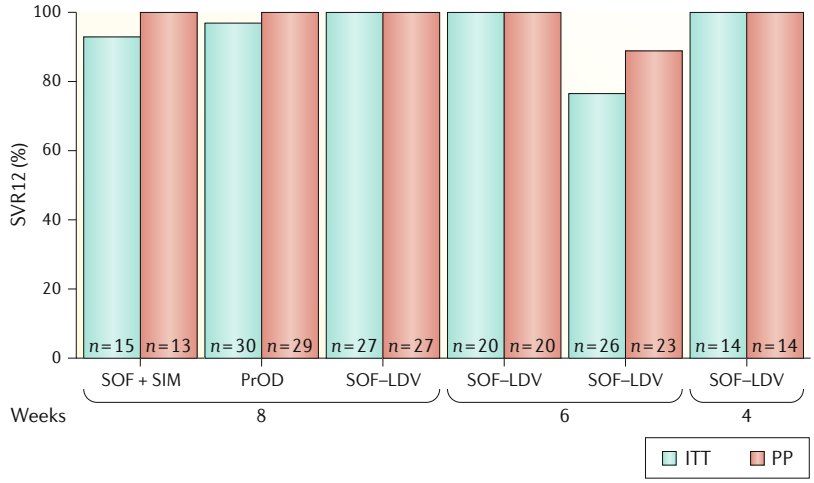

Fig. 2 | **Efficacy of shortened duration direct-acting antiviral agent therapy in acute and recent HCV genotype 1 infection.** The studies presented tested dual-class or triple-class direct-acting antiviral agent therapy in acute and recent HCV genotype 1 infection by intention-to-treat (ITT) and per-protocol (PP) analysis. PrOD, paritaprevir–ritonavir–ombitasvir and dasabuvir; SIM, simeprevir; SOF, sofosbuvir; SOF–LDV, sofosbuvir–ledipasvir; SVR12, SVR at 12 weeks. Data from REFS[169,171,173].

pan-genotypic DAAs in well-characterized populations (including people with HIV infection or PWID) will be extremely valuable in determining the utility of DAAs in recent HCV infection. With high HCV infection incidence in populations of PWID and HIV-positive MSM, determining the optimal timing of treatment initiation, duration of therapy and regimen choice in recent infection is important (including for treatment of reinfection). If ultra-short duration therapy with an optimal DAA regimen is shown to be highly effective in individuals in the first year after infection acquisition, this finding will have major implications for screening and treatment strategies in high-risk populations.

Reinfection after treatment

One challenge to HCV elimination is reinfection. Higher HCV reinfection incidence after treatment in acute HCV cohorts (reinfection incidence 7.4–15.2 per 100 person-years)[68,185–187] (TABLE 3) contrasts with the majority of published and preliminary studies among individuals treated for chronic HCV infection (reinfection incidence 0–5 per 100 person-years)[188–190]. The risk of reinfection after treatment for both acute and chronic HCV infection is higher in those who report ongoing high-risk behaviour (such as continued injection drug use)[187,189,191–193], highlighting the need for post-treatment surveillance, rapid diagnosis of reinfection and access to re-treatment.

Although injecting risk behaviour among PWID seemed to decline following interferon-based treatment[194–196], it is possible that expanded HCV treatment access and DAA therapeutic optimism might be associated with increased risk behaviour, as seen among MSM following the introduction of HIV combination antiretroviral therapy[197]. The incidence of HCV reinfection will require robust evaluation with sufficient follow-up time and HCV RNA testing at regular intervals. Although annual HCV RNA testing is recommended to monitor at-risk individuals, the optimal interval (3, 6 or 12 months) for repeated HCV RNA testing requires investigation, as testing frequency will affect reinfection detection[198]. Routine post-treatment surveillance should ensure that reinfection is diagnosed within the first year of re-acquisition, which will have substantial implications for therapeutic strategies in recent HCV infection. Additionally, characterization of reinfection and the host–virus interplay in the setting of re-exposure might assist in vaccine development.

As DAA treatment scale-up expands among populations exhibiting ongoing risk behaviours for reacquisition (including recent PWID and HIV-positive MSM), acknowledgement that HCV reinfection can and will occur is essential. HCV reinfection prevention and management strategies should be incorporated into the individual-level and population-level HCV responses (BOX 3). Options include education and counselling[199], optimal harm reduction[36,46,53,58–60,62,65,200], treatment of the individual and their injecting (or sexual) partner or people in their network[201], management of medical and psychiatric comorbidity[62], post-treatment surveillance[202] and rapid re-treatment of reinfection. At a population level, universal access to care and treatment, political will, sufficient funding and alleviation of the stigma associated with HCV infection should assist in efforts to reduce HCV primary and reinfection incidence. Most importantly, re-treatment for reinfection should be offered without stigma or discrimination.

HCV treatment as prevention

The availability of DAAs has provided the therapeutic tools required to strive for HCV elimination and has stimulated discussion around HCV treatment as prevention[8]. To achieve elimination, strategies to curb transmission will be required. One approach to reduce transmission is improved diagnosis and treatment of recent HCV infection. Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence can be achieved by targeted DAA treatment scale-up among those at highest risk of ongoing transmission, including PWID and HIV-positive MSM[11,203–206]. Data from the UK Collaborative HIV Cohort predicted that the greatest effect on HCV incidence and prevalence would be achieved if DAA scale-up was prioritized to those with recently diagnosed (<1 year) HCV infection and if it occurred in combination with behavioural interventions[11]. Despite the high cost of DAAs, treating recent PWID and HIV-positive MSM with early liver disease associated with HCV infection seems to be cost-effective given the reduction in liver-related complications and additional benefit of averting secondary infections[9,207,208]. In jurisdictions with universal access to DAAs, encouraging initial reports highlight high DAA uptake among HIV-positive MSM, with corresponding reductions in HCV viraemic prevalence[209,210] and incidence[209]. Modelling estimates and real-world data support broad access to DAAs, without limitations based on duration of infection, disease stage or drug use, to gain the greatest individual-level and population-level benefits.

Table 3 | **HCV reinfection after treatment for acute and recent HCV infection**

Author, year	Study population (% total study population)	Location, study design	*n*	Reinfection (*n*)	PYFU	Reinfection incidence per 100 person-years (95% CI)
Meta-analyses						
Hagan, 2015 (REF.[68])	HIV-positive MSM (100%)	NA, meta-analysis (pooled results of two studies)	170	38	NA	11.4 (7.4–17.7)
Primary studies						
Lambers[a], 2011 (REF.[185])	HIV-positive MSM (100%)	Netherlands, retrospective	56	11	72	15.2 (8.0–26.5)
Martin[a], 2013 (REF.[186])	HIV-positive MSM (100%)	England, retrospective	114	27	NA	9.6 (6.6–14.1)
Vanhommerig, 2014 (REF.[232])	HIV-positive MSM (100%)	Netherlands, prospective	35	16	NA	NA
Martinello, 2017 (REF.[187])	HIV-positive MSM (53%) and recent PWID (49%)	Australia, prospective	120	10	135	7.4 (4.0–13.8)

MSM, men who have sex with men; NA, not available; PWID, people who inject drugs; PY, person-years; PYFU, person-years follow-up. [a]Studies included in the meta-analysis performed by Hagan et al.[68].

Recommendations

Management of recent HCV infection in the era of DAAs. Interferon-free DAA therapy is not currently approved by regulatory authorities for use in acute HCV infection. Although encouraging results following short duration therapy have been obtained in small cohorts[169,170], enrolment in prospective clinical trials is recommended to confirm this strategy. Pending the results of these clinical trials, people with acute HCV infection might be considered for treatment with the same DAA regimens as recommended for chronic HCV infection. Monitoring HCV RNA titres for 4–12 weeks following diagnosis of acute infection provides an opportunity to assess for spontaneous clearance before treatment initiation[156–158]. Given the individual-level and population-level benefits, access to HCV care and treatment for people at high risk of onward transmission, including those with recent HCV infection, should be a priority[8].

Screening strategies in high-risk populations. Greater HCV testing (increasing access as well as regular testing and follow-up), diagnosis and linkage to care are required to facilitate DAA treatment scale-up. All PWID and HIV-positive MSM should be screened for HCV infection with anti-HCV antibody[102,105,129,130]. In the context of ongoing risk behaviour (injection drug use and/or high-risk sexual behaviour), anti-HCV antibody screening every 6–12 months should be performed to assess for incident infection[102,105,129], with supplemental testing following potential exposure[130]. Assessment of HCV viraemia with HCV RNA should occur if there is high clinical suspicion, if transaminase (particularly ALT) levels are elevated or if HCV reinfection is suspected. Screening protocols for recent HCV infection in specific high-risk populations, including young PWID[55,139,211], PWID in incarceration[41,212] and HIV-positive MSM[69,213], should be considered[214,215], potentially utilizing rapid or point-of-care diagnostics[118,119,121,216], to improve HCV diagnosis, prevention and surveillance.

Box 3 | **Strategies to reduce HCV reinfection**

- Harm reduction[36,46,53,58–60,62,65,200]
  - Needle and syringe programme
  - Opioid substitution therapy
- Integrated care[62,201,228]
  - Mental health assessment
- Education[229,230]
  - Counselling
  - Peer support
- Post-treatment surveillance[102,105,129,202]
  - Regular HCV RNA testing
- Re-treatment of reinfection

Conclusions

The advent of highly effective, well-tolerated interferon-free DAA therapy has revolutionized HCV therapeutics[16]. Combining two or more potent DAAs from different classes has increased SVR (>90%) and shortened treatment duration to only 8–12 weeks in most populations with chronic HCV infection. Excellent results in chronic HCV infection have lessened the potential 'efficacy advantage' of early treatment initiation in acute HCV infection, but diagnosis and treatment of recent HCV infection should facilitate engagement in multidisciplinary care, prevent the development and complications of chronic liver disease and curb ongoing transmission in key populations. The role of ultra-short duration DAA therapy in recent HCV infection requires further evaluation.

The burden of disease attributed to HCV is high among PWID and is increasing among HIV-infected MSM. The potential for broad access, rapid DAA treatment scale-up and further treatment simplification has stimulated discussion around HCV treatment as prevention and HCV elimination[8]. HCV treatment as prevention strategies will be improved by early

diagnosis and increased treatment uptake in recent HCV infection[11,203]. Ultimately, the population-level effects of DAA therapy will relate to facilitating global access to HCV screening, care and treatment[217]. The risk of HCV reinfection following treatment in individuals with ongoing behaviour facilitating HCV transmission emphasizes the need for post-treatment surveillance, harm reduction strategies and education but must not be considered an impediment to treatment if HCV elimination is to be achieved.

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Review criteria
Data for this Review were identified by searches of PubMed and Google Scholar up to 24 October 2017 using the terms "acute hepatitis C", "acute HCV", "recent hepatitis C", "recent HCV", "early hepatitis C" and "early HCV" in combination with the roots "epidemi*", "diagnos*" "natural history", "spontaneous clear*", "HIV", "men-who-have-sex-with-men", "men who have sex with men", "MSM", "inject drug*", "injecting drug*", "drug inject*", "drug use*", "PWID", "treat*", "direct acting antiviral*", "direct-acting antiviral*", "DAA", "interferon free", "interferon-free", "IFN free" and "IFNfree". No language or date restrictions were specified. The references of identified articles were manually searched for further relevant papers. Key abstracts at international meetings were also considered. ClinicalTrials.gov was searched for studies in progress.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41575-018-0026-5.