Editorial

Hepatitis C—committing the world to an eradication of the infection

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In a current issue of *The Lancet*, Spearman and colleagues have provided an extensive global review on hepatitis C virus (HCV) infection, which covers important aspects of epidemiology, natural history, key populations at risk for the infection, aspects on screening and linkage to care and finally current treatment options (1).

Important key messages of the article can be summarized as follows:

(I) Chronic hepatitis C has changed from an incurable to a curable disease in only 25 years after identification of the virus. In clinical practice, there is almost no scenario any more in which treatment options with cure rates >95% could not be offered. This even holds true for formerly "difficult to treat patients" like individuals with liver cirrhosis, end stage renal disease and hemodialysis, people who inject drugs (PWID), cases with solid organ transplantation, or patients with psychiatric comorbidities.

(II) DAA treatment is safe, without significant side effects in the majority of patients, and easy to perform as oral regimens. Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir are the preferred co-formulated therapies with pan-genotypic efficacy in treatment naïve and interferon-experienced patients over almost the entire disease spectrum from absence of liver fibrosis until compensated cirrhosis. Sofosbuvir/daclatasvir is another pan-genotypic treatment alternative which is frequently used in low- and middle-income countries. The use of ribavirin can be restricted to single cases which is a major advantage concerning tolerability of antiviral therapy.

Patients with advanced fibrosis or cirrhosis with cure after DAA therapy should undergo surveillance for hepatocellular carcinoma every 6 months, because HCV-induced epigenetic changes associated with HCC-risk persist after sustained virologic response (2).

The advantages of modern DAA treatment strategies allowed the World Health Organization (WHO) to postulate a global hepatitis C strategy which aims to eliminate the infection as a public health threat until the year 2030. This includes introduction of blood and injection safety and harm reduction initiatives to reduce the HCV incidence by 80%, diagnose 90% of the HCV infected population, treat 80% of the eligible patients and reduce liver-related death by 65% by 2030. Already few years after the introduction of DAAs reduction in HCV-associated morbidity and mortality can be observed (3).

However, although the DAA regimens offer excellent prerequisites to eliminate HCV infection, the WHO target will not be met by the majority of high-income countries within the next decade: only 9/45 countries are currently on track to achieve the WHO goals (4). Razavi *et al.* propose eight key factors for HCV elimination which include political will, finance a national program, implement harm-reduction programs, expand treatment capacities beyond specialists, remove treatment restrictions, implement monitoring and evaluation, screening and awareness, and linkage to care. The three most important elements of this strategy are political will, removal of treatment restrictions, and monitoring and evaluation of existing programs, which may be accompanied by prevention and harm reduction.

The current key populations at risk for HCV infection are PWID, men who have sex with men (MSM), incarcerated people, and patients who undergo invasive medical

procedures with inadequate hygienic precautions in low- and middle-income countries (1). Awareness of HCV infection and harm reduction programs are important aspects in these risk groups: PWID who recently started injecting drugs have a low awareness of their HCV status, but more than 80% have attended low-threshold drug services during the last month (5)—a setting, in which more knowledge about HCV and its risk factors and capacity for point of care test systems should be established (1). As HCV-RNA is detectable in nasal and rectal fluid in patients with high viral blood load awareness of these potential source of HCV transmission and adequate precautions (i.e., clean drug preparing devices and nasal drug sniffing tools in addition to needle and syringe exchange programs or use of condoms during sexual intercourse with high-risk partner) are of upmost importance (6). In the MSM community, chemsex practices with sex-enhancing drugs in combination with specific sexual and social behaviors have gained popularity and are associated with increased risk for HCV infection and condom-less sex (7). For the populations with repetitive risk behavior like MSM or PWID it is important to emphasize that DAA therapies of chronic HCV infection promise high cure rates, but do not provide immunity which would prevent re-infection. In fact, HCV re-infections in MSM after successful DAA treatment are frequently observed (9.02 per 100 py), and 15% of cases are HCV-RNA positive again after an observation period of less than 2 years (8). The re-infection incidence rates in the MSM community are 3- to 10-fold higher in the DAA era than the estimated primary incidence rates in the same settings, illustrating that DAA therapy alone is insufficient to overcome the HCV epidemic, but that prevention strategies need to be adapted to the ongoing high-risk transmission behaviors (8,9).

In PWID, two recent meta-analyses have analyzed efficacy and re-infections rates in the DAA era (10,11). The pooled sustained virologic response rates were 88% and 90–91% in patients on opioid substitution therapy (OST). Treatment discontinuation rates and incidence of re-infection (1.94 per 100 py) were low indicating that people who report recent injecting or OST recipients should not be excluded from HCV therapy. However, PWID populations are heterogeneous (i.e., active or unstable iv-drug user *vs.* former PWID), and re-infection rates will increase if larger population with high-risk behavior will be treated: In Scotland, the HCV re-infection incidence rate was 34.6 per 100 py in active PWID under the age of 30 (12). Nevertheless, achievement of HCV elimination goals and especially reduction of HCV incidence rates will demand treatment in exactly these provoking populations (13). HCV dynamics among PWID suggest that an annual treatment uptake above 10% would eliminate the disease by 2030 (14).

Concerning HCV infected patients in prison, Spearman *et al.* have already discussed efficacy and cost-effectiveness of OST and needle and syringe exchange programs, and the insufficient political support of such harm-reductions interventions in many countries (1). A recent review points out that according to Universal Declaration of Human Rights and by the International Convention on Economic, Social and Cultural Rights people living in prison should receive the same health care as people outside of prison. However, even in an enlightened country such as Germany a non-supply of OST in prisons is often guided by ideology, morally driven arguments, and social determinants, but not by science and evidence (15).

A positive example of the beneficial effect of a consensus political will to eradicate HCV infection and of a continuous re-evaluation of the initiative is the national program of Georgia (16). Within a couple of years approximately one-third of the infected patients was treated and achieved SVR-rates of 98.5%. The country established reflex-testing with HCV core antigen tests in anti-HCV positive individuals, because over 20% of anti-HCV positive screening cases failed to receive further diagnostic testing to proof active HCV infection. This strategy doubled the rate of persons receiving viremia diagnostics, however, rates of treatment initiation among those diagnosed in the reflex testing approach were lower than those in other settings, which may be a consequence on how individuals were informed and counseled about their infection. These unforeseen results are now actively addressed (16).

The US approach of HCV testing in baby boomers born from 1945 to 1965 increased screening activities from 10% to 35% (17). Whether this success translates in better linkage to care, higher treatment uptake, and finally reduction of HCV related mortality has to be investigated in the future.

A negative example of political interventions which demands the necessity of re-evaluation is a laboratory reform of the medical self-government in Germany which turned anti-HCV from an extra-budgetary reimbursed screening parameter to a budgetary relevant laboratory test in the outpatient setting leading to almost 10% fewer anti-HCV tests within only 1 year. This policy directly counteracts the WHO and German government strategies to eliminate hepatitis C (18).

In summary, the hepatitis C article of Spearman *et al.* is a comprehensive review about the current global situation of hepatitis C (1). The WHO 2030 HCV elimination target

is an important political initiative which has triggered multiple programs all over the world. Even if the HCV elimination target will not be globally achieved until 2030, patients, physicians, politicians, and stakeholders have been sensitized to sustainably tackle the infection.

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