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The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations

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Abstract (150/150 word max)

The introduction of efficacious new hepatitis C virus (HCV) treatments galvanized the World Health Organization to define ambitious targets for eliminating HCV as a public health threat by 2030. Formidable obstacles to reaching this goal can best be overcome through a micro-elimination approach, which entails pursuing elimination goals in discrete populations through multi-stakeholder initiatives that tailor interventions to the needs of these populations. Micro-elimination is less daunting, less complex, and less costly than full-scale, country-level initiatives to eliminate HCV, and can build momentum by producing small victories that inspire more ambitious efforts. The micro-elimination approach encourages stakeholders who are most knowledgeable about specific populations to engage with each other, and also promotes the uptake of new models of care. Examples of micro-elimination target populations include medical patients, people who inject drugs, migrants and prisoners, although candidate populations can be expected to vary greatly in different countries and sub-national areas.

Introduction

The introduction of direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection in 2013 is one of the greatest advances of the current biomedical era. Treatment with DAAs achieves sustained virologic response (SVR) rates of ≥95% after 8–12 weeks of treatment for one of the leading causes of chronic liver disease and liver-related deaths worldwide. [1] [2] [3] The efficacy of the new DAA treatment regimens galvanized the World Health Organization (WHO) to adopt its first-ever *Global Health Sector Strategy on Viral Hepatitis* in 2016. The strategy defines ambitious time-bound targets for eliminating HCV as a public health threat by 2030. One key target is for countries worldwide to reduce new HCV cases by 80% and another is to reduce HCV-related deaths by 65% by 2030.[1]

Scaling up DAA treatment is essential for achieving the HCV targets, but this constitutes an enormous public health challenge. A major obstacle is underdiagnosis: only 20% of people with HCV worldwide have been diagnosed.[2] While approximately 71 million people were thought to be infected with HCV in 2015, only 1.76 million people received HCV treatment in 2016.[1] Three quarters of people with HCV live in low- and middle-income countries[5], many of which lack the resources to stage major HCV testing and treatment campaigns. In January 2018, the Polaris Observatory reported that only nine countries were on track to meet the 2030 WHO HCV elimination targets: Australia, Egypt, France, Georgia, Germany, Iceland, Japan, the Netherlands, and Qatar.[2]

What is the micro-elimination approach to eliminating HCV?

In 2017, the European Association for the Study of the Liver's International Liver Foundation suggested that stakeholders can best grapple with the complexity of the HCV elimination challenge by setting micro-elimination goals – "break[ing] down national elimination goals into smaller goals for individual population segments, for which treatment and prevention interventions can be delivered more quickly and efficiently using targeted methods."[1] The following review builds on this concept by distinguishing a *micro-elimination approach* from efforts to merely reduce HCV prevalence, incidence, and mortality in specific populations. Generally speaking, micro-elimination approaches should meet the following criteria, although these criteria may need to be adapted to different epidemiologic situations and geographic settings:

1. There is a plan for how to tailor health resources and services to overcome known barriers and achieve high levels of HCV diagnosis and treatment in one or more clearly definable populations of interest within a specified timeframe.
2. The plan sets forth achievable annual targets, basing these on mathematical modeling when relevant to determine the levels of diagnosis and treatment required to progress to the plan's ultimate elimination targets.
3. The plan is developed and implemented through a multi-stakeholder process, with essential participants including government officials, health service providers, and civil society representatives.
4. Progress and outcomes are monitored and publicly reported using indicators selected at the outset of the process.

There can be a great deal of variation in the geographic scope of micro-elimination efforts. In some cases, it might be logical to pursue micro-elimination in a specific population nationally, while in other cases there are reasons to work on a smaller scale, such as regionally or at the city level. An initiative employing a micro-elimination approach might focus on only one population, or it might focus on all of the populations affected by HCV within a designated geographic area. In cases in which comprehensive national HCV elimination efforts are proposed or underway, such as in Iceland (Box 1), it may be the case that these efforts encompass multiple micro-elimination approaches. For the sake of conceptual clarity, however, we propose that efforts to eliminate HCV in *all* populations at the national level not be considered micro-elimination, even when the country has a very small population.

Activities targeting some of the smallest sub-populations of HCV-infected people, such as an initiative to cure HCV in all patients attending a single health clinic, would make welcome contributions to HCV elimination but might not actually embody the micro-elimination approach if the task at hand does not require a multi-stakeholder planning and implementation process. On the other hand, an effort to eliminate HCV in a population of the same size at a single prison would constitute micro-elimination if stakeholders engage in this undertaking in a way that embodies the aforementioned criteria. The micro-elimination approach particularly emphasizes choosing the interventions that are most relevant to the population of interest, tailoring these interventions in accordance with evidence about the population's needs, and tracking how the interventions contribute to progress toward publicly agreed-upon elimination goals. Preferably, those goals would align with the global goals set by WHO.[4]

While pursuing a micro-elimination strategy requires grouping people with HCV infection into different populations, some individuals are in reality members of more than one population. Hence, an HCV-infected migrant who injects drugs, for example, might be engaged in care through more than one micro-elimination pathway. At the same time, multiple pathways might be required to reach different subgroups within the same population. A micro-elimination program targeting people who inject drugs (PWID), for example, might need to use different types of service delivery models for PWID who are receiving opioid substitution therapy and those who are not, or for PWID who are incarcerated versus those in the community.

HCV-infected children fall into many of the populations described in this article as potential micro-elimination targets, including aboriginal and indigenous communities, migrants, and PWID. It is important to consider the ways in which children and adults differ from each other in regard to their HCV prevention and treatment needs (Box 2). Women of childbearing age are another group that warrants special consideration across micro-elimination initiatives in different populations. The estimated global number of women of childbearing age (aged 15–44 years) who have HCV viremia is 13.0 million[1], with injecting drug use thought to account for increasing numbers of infected women and children in some settings in recent years.[1 2] Children and women of childbearing age, generally speaking, may not be practical micro-elimination targets because both populations are so large and diverse that tailored interventions would still be needed for many different subpopulations. It is advisable for micro-elimination strategies targeting almost all populations to take into account whether the needs of children and women of childbearing age within those

populations are being addressed. In some settings, HCV epidemic dynamics might argue in favor of developing micro-elimination initiatives specifically targeting populations such as children receiving inpatient hospital care or women of childbearing age in prisons, to name two of many possible examples.

The micro-elimination approach is not meant to override medical and ethical standards widely endorsed by the global community of HCV stakeholders; it is instead offered to aid strategic decision-making in situations where the most appropriate use of resources is not already clear. Furthermore, as everyone holds the same human rights to health services, it is essential to provide a strong rationale for why some populations are being chosen over others for micro-elimination programs, along with a commitment to address the HCV-related needs of those other populations in conjunction with pursuing micro-elimination. International human rights standards in fact call for governments that prioritize the allocation of limited health resources to specific populations to set targets for when those resources will reach everyone in need – a concept known as progressive realization.[1] In other words, a health system cannot use a micro-elimination initiative targeting patients undergoing hemodialysis, for example, as an excuse to turn its back on HCV-infected PWID or migrants. National and subnational HCV elimination plans must take into account all HCV-affected populations and must set goals and targets accordingly; the micro-elimination approach merely constitutes a method of focusing and organizing on-the-ground activities in order to take tangible steps toward the larger goal of eliminating HCV in the entire population.[2]

An essential component of HCV elimination is reducing transmission by infected people who have not yet been treated or not responded to treatment. Prevention thus needs to remain a prominent element of national and subnational responses to HCV. There are large gaps in HCV prevention services in many low- and middle-income countries (LMIC) with high HCV prevalence. As a global micro-elimination agenda emerges, this agenda must not be permitted to draw attention and resources away from some of the most basic HCV prevention needs of LMIC. For example, there are unrealized opportunities to reduce nosocomial transmission of HCV in some LMIC.[2] Further, many LMIC have yet to acknowledge the importance of PWID populations in their countries. As such there is a dearth of needle and syringe programs and opioid substitution therapy services.[2] The global community of HCV stakeholders, including funders, should make it a priority to foster health system policies and interventions addressing HCV prevention.

Why take a micro-elimination approach?

The challenges associated with eliminating HCV encompass both logistic and political considerations: many health systems are not prepared to massively increase HCV prevention, testing and treatment activities, while many stakeholders who influence the allocation of financial and human resources are not convinced of the need to prioritize HCV or are unable to come to an agreement on how HCV elimination targets should be pursued. The micro-elimination approach can present many pathways for overcoming these issues. Micro-elimination is likely to strike stakeholders as less daunting, less complex, and less costly than full-scale country-level initiatives to comprehensively eliminate HCV. In the many countries that have not formally established the goal of HCV elimination, setting and

achieving micro-elimination goals can serve as a step in this direction, with early successes inspiring more ambitious efforts.

From a public health standpoint, a key feature of HCV is that its diverse transmission routes have resulted in the spread of the disease among a wide range of populations. The micro-elimination approach encourages stakeholders who are the most knowledgeable about specific populations to engage with each other. Having the goal of eliminating HCV among all patients on hemodialysis nationally, for example, might foster collaboration among diverse stakeholders who can help drive progress, including different types of clinical specialists, various cadres of health-care workers, public health officials and patient groups. Furthermore, organizing around micro-elimination goals could create opportunities for cross-border collaboration, e.g., hemophilia patient groups working at a regional or global level might be asked by their in-country counterparts to help lobby governments to adopt micro-elimination targets. A micro-elimination approach could also encourage the uptake of new models of care, such as the co-location of services or shifting of HCV testing and treatment sites to different hospital departments or outside of hospital settings.[2 3 4 5 6]

Micro-elimination approaches in populations at high risk of transmitting HCV can potentially contribute to "treatment as prevention".[2] The concept of treatment as prevention is to successfully treat an HCV-infected person who is at risk of passing the virus on to others and eliminate the possibility of further transmission, thereby achieving "prevention." While there is not yet a real-world demonstration of the potency of treatment as prevention, modeling indicates that carrying out this strategy on a sufficiently large scale accelerates progression to population elimination, with especially notable gains seen when PWID are the focus in HCV epidemics driven by injecting drug use.[2 3] In other words, if a large proportion of HCV-infected PWID in a specific geographic area undergo successful treatment and achieve SVR, this will result in a sharp drop in the number of HCV-infected people who have the potential to transmit the disease to others with whom they share injecting equipment.[20] The aim of treatment as prevention is to successfully treat enough people to reach a threshold where new infections are greatly reduced. Because of the potential to prevent further infections, many of which would incur the high costs of treating end-stage liver disease, models suggest that high levels of treatment combined with other preventive measures may prove cost effective, especially if indirect costs such as loss of earnings due to disability are considered.[2 3]

While a micro-elimination approach is not required to take advantage of treatment as prevention, it presents the opportunity to comprehensively engage in processes that make treatment as prevention more likely to be successful, e.g., the involvement of a broad coalition of stakeholders and the careful tracking of changes in HCV incidence and prevalence.

Which populations should be targeted for micro-elimination?

Candidate populations for micro-elimination approaches can be expected to vary greatly in accordance with the epidemiology and health context of different countries and sub-national areas. In this review, we discuss key features of 10 candidate populations. Other populations also warrant attention, and researchers and technical experts are encouraged to publish information about all potential micro-elimination populations in order to move this

aspect of HCV elimination forward. Given that affected populations are not the same across all countries, the following subsections are arranged alphabetically to avoid the implication that some populations should be uniformly prioritised above others.

Aboriginal and indigenous communities

Some aboriginal and indigenous communities are disproportionately affected by HCV, including communities in Australia[2], Canada and the United States. For example, the acute HCV infection rate for American Indian and Alaska Native (AI/AN) populations was approximately twofold higher than that of non-Hispanic whites in 2015, while the HCV-associated mortality rate was threefold higher than that of non-Hispanic whites.[2] Studies have indicated that HCV prevalence may be three to eight times higher in some Aboriginal Canadian populations than in non-Aboriginal Canadian populations.[2 3] While there are limited data from Latin America, a Colombian study found 5.7% HCV antibody prevalence among Amerindians belonging to four ethnic groups.[2] In contrast, overall HCV antibody prevalence in Columbia is estimated to be 1.1%.[2]

Isolation, rural location, poverty, and communication barriers as well as cultural beliefs can all contribute to lack of testing and treatment uptake in aboriginal and indigenous populations.[2 3] Studies in Australia and the United States have documented good outcomes for HCV testing and treatment programs targeting aboriginal and AI/AN populations,[2 3] and the success of one US initiative led to the launch of the Cherokee Nation HCV elimination program in 2015.[4] There appears to be little other research to guide the design of HCV elimination interventions for aboriginal and indigenous communities.

Birth cohorts with high HCV prevalence

In most countries, a group of people born in a specific span of years has a higher prevalence of HCV infection than the general population. This group is known as a “birth cohort.” This “cohort-effect” occurs due to changing infection modes. In some countries, for instance, many HCV infections are attributable to unsafe medical procedures that were largely eliminated when the danger was recognized and better infection control measures were put into place.[2] The span of cohorts affected varies across countries.[2 3 4] While in the United States people born from 1945 to 1965 are at higher risk[26], the Mexican cohort is older[37], the Czech Republic’s is younger[36], and Poland appears to have no correlation between age and HCV prevalence.[2] The possible existence of an at-risk birth cohort thus needs to be investigated on a country-by-country basis. In countries where there are birth cohorts with high HCV prevalence, a key advantage of birth-cohort testing is that it removes potential stigma from testing, as everyone within the age group is tested regardless of behavior, removing the perception of blame.[2] A review examining the cost–effectiveness of interventions, which included eight studies evaluating birth cohorts in four countries (all with known high-risk birth cohorts approximately 50 years of age and older), found that in all instances, birth-cohort testing was cost effective when compared to either the status quo or even risk-based testing.[40] Similar results were found in Switzerland where far fewer people needed to be screened in specific cohorts to find one new HCV infection as compared to the general population.[38] Despite this, global stakeholders have been slow to add birth-cohort analysis to their recommendations, and the first-ever WHO Global Health Sector Strategy on Hepatitis 2016–21 fails to make any mention of it.[4] One-time HCV testing of

patients in high-risk cohorts has been recommended for both the United States and European countries,[2] and may be found useful in countries with a clearly identifiable at-risk birth cohort. However, defining this cohort requires population-based seroprevalence data, and not many countries have conducted the large and expensive national surveys that are required to obtain these data.

Children of HCV-infected mothers

Mother-to-child transmission of HCV is the primary mode of infection for children. According to a 2014 systematic review, there is a 5.8% risk of mother-to-child HCV transmission among HIV-negative women, and a 10.8% risk among HIV-positive women.[2] Although this represents a low transmission risk per individual case, mother-to-child transmission still may add considerably to the burden of HCV disease. Unfortunately, there are several barriers to both identification and treatment in this group. Although RNA testing is accurate as early as two months of age, antibody testing of infants less than 15 months of age is complicated by maternal antibodies.[2 3] A prospective study in Tennessee found that more than half of the infants of infected mothers left pediatric care prior to the 18-month appointment at which they would be tested for HCV[2], indicating that loss to follow-up is potentially a major challenge in this population. Furthermore, although DAAs have been approved in children aged 12–17 years, studies for younger children have not yet been completed.[44] Because of these limitations, infected children are likely to remain infected for an extended time, making it all the more important that they receive regular liver function tests and HCV RNA quantification until they reach an age at which they are eligible for treatment with DAAs.[44]

Regarding the issue of how more HCV-infected children can be diagnosed, current World Health Organization guidelines recommend against routinely testing pregnant women in the general population for HCV[2], reflecting the lack of evidence of this approach being cost-effective.[2] In the context of developing micro-elimination strategies targeting children in specific settings, it may be advisable to consider the possible role of universal screening of pregnant women in those settings. This is a rapidly evolving area of research, and new evidence may influence changes in guidelines and best practices.

Hemodialysis recipients

The transmission of HCV to hemodialysis patients has declined over the years due to better screening of blood products, improved dialysis procedures, and less need for blood transfusion with the availability of erythropoiesis—stimulating agents. Nonetheless, HCV prevalence remains far higher in people receiving hemodialysis than in the general population.[2 3 4] In lower-income countries, both transfusion of contaminated blood products and hand-borne nosocomial transmission continue to be major infection pathways[13], but for higher-income countries the latter is currently the key pathway.[2] Interferon-based therapies are not well tolerated by hemodialysis patients, as reflected in treatment rates of 1–4% in high-income countries.[51 2 3] DAAs, however, are proving to be well tolerated and effective in this population.[49 2 3] Furthermore, because patients with chronic kidney disease and HCV infection may lose kidney function at an accelerated rate compared to HCV-negative patients, and because HCV can cause complications in post-kidney-transplant patients, it is often recommended that patients receive treatment prior to transplantation[53 2 3], unless an HCV-infected graft is rapidly available and HCV treatment can be provided following

transplantation. Since acute HCV infection is frequently asymptomatic, regular screening is advised from the start of maintenance hemodialysis.[49 2] Spontaneous clearance is rare among hemodialysis patients, so treatment should be provided as soon as possible.[51] Thorough training and strict adherence to infection control protocols by staff are necessary to prevent future infections.[48 58] There is a need for rigorous screening to ensure that no new recipients of hemodialysis are infected with HCV, since such cases would allow for the reintroduction of HCV in hemodialysis units where progress had been made toward HCV elimination. The widespread treatment of HCV in people receiving hemodialysis will likely achieve the "treatment as prevention" outcome of reducing the incidence of transmission in hemodialysis units when paired with appropriate prevention measures.[2]

HIV/HCV-coinfected people

It is estimated that worldwide, at least 2.3 million people are coinfected with HIV/HCV.[2] People come to be coinfected with HIV/HCV via various pathways, often related to ongoing risk factors; common modes of transmission include the use of unsterile injecting drug equipment and sexual transmission between men. Reinfection is a particular challenge in men who have sex with men (MSM), with a reinfection rate of 25% observed in a large Western European cohort after two years of follow-up.[2] Regular testing is therefore recommended. Since HIV therapy needs to be given lifelong, and follow-up visits are regularly scheduled, such patients are readily available for testing and, if necessary, treatment for HCV. Furthermore, two studies from the Netherlands and Switzerland have shown that high rates of DAA treatment uptake by their HIV/HCV-coinfected cohorts reduced new acute HCV infections in MSM by around 50%[3 4], leading to the possibility of treatment as prevention and making elimination far more feasible. Coinfection with HIV does not impact the effectiveness of HCV treatment: equally high SVR rates can be found in HIV/HCV-coinfected patients as in HCV-monoinfected patients.[3, 4]

Migrants from high-prevalence countries

Due to risk factors such as HCV prevalence in their country of origin, countries visited during their journey as migrants, and the conditions they experienced during migration, immigrants and refugees (collectively referred to in this article as migrants) are at elevated risk of being infected with HCV as well as having other health problems. Migrants often remain unidentified and thus untreated. According to a 2015 review, anti-HCV prevalence among migrants was 1.9% overall, with higher rates associated with region of origin, particularly Eastern Europe, Asia, and Sub-Saharan Africa.[2] Factors that often limit HCV testing in migrant populations include lack of knowledge about where and how to get tested, concern for how a positive result might affect the host country's acceptance, lack of primary health care, and providers' possible reluctance to test for chronic conditions in patients they may never see again.[3] Furthermore, because they may not belong to populations that the host country considers to be at high risk, current screening practices may allow migrants to fall through the cracks and remain untested.[66 3] Although migration status in and of itself is not an indicator for HCV, region of origin is; migrants from countries with a high and moderate prevalence of HCV are at greater risk of infection.[68] There have been some efforts to reach this marginalized population. An HCV screening program started in southern Italy in 2012[2] not only tested undocumented immigrants and low-income refugees, but offered treatment and linkage to care, showing that it was possible to identify and retain migrant patients

throughout the testing and treatment process.[67] Another Italian study, based in Palermo, retained 87% of patients and achieved SVR in 100% of the treated patients.[2] A successful micro-intervention strategy targeting migrants from high-prevalence countries must include provision for screening and linkage to care, as well as cultural mediators for translation and explanation of the importance of screening and treatment.[69]

People who inject drugs

Globally, PWID account for 8% of all chronic HCV infections and 23% of new infections[5], making them a large and growing segment of the HCV burden. They are a particularly important population to treat, both because of their high prevalence and the dynamic spread of infection among the larger population.[2] This situation makes it likely that "treatment as prevention" will need to play a key role in eliminating HCV in PWID. Unfortunately, because injection drug use is often stigmatized and even illegal, PWID are less likely to seek out or accept medical help. Health systems, often government provided, frequently impose barriers relating to a lack of housing or a permanent address; are inflexible with locations and appointment times; and are physically distant from the person, with travel costs being a disproportionate burden. Some countries also do not provide antiviral treatment to current drug users. There is, however, extensive evidence that PWID can be effectively targeted and treated. [20 2 3 4] For example, studies in Scotland and Iceland found that it was possible to cure active drug users of HCV;[2 3] nurse-led models of care have proved efficacious in improving access to care and successful treatment outcomes[2 3], and a community-based public health facility in Sydney, Australia found that PWID can be successfully treated for HCV using an integrated primary health-care model. It also demonstrated the feasibility of scaling up DAA therapy in high-risk PWID populations, with potential individual and population-level public health benefits.[2]

PWID populations need specific care pathways for HCV diagnosis and treatment, and these pathways should be based around facilities and services that they are already accessing. Because many PWID already utilize opioid substitution therapy as well as needle and syringe programs, the facilities and locations where these interventions and treatments take place are ideal for new HCV diagnosis and treatment initiatives. There are also models for engaging PWID who do not seek out these services. In Iceland, for example, the national HCV elimination program has targeted homeless shelters as part of its extensive outreach measures.[2] HCV treatment should be provided to PWID as part of the comprehensive package of interventions recommended by WHO, UNAIDS and the United Nations Office on Drugs and Crime for HIV prevention, treatment and care for injecting drug users. This landmark guidance document calls for viral hepatitis prevention, vaccination, diagnosis and treatment along with key harm reduction services such as opioid substitution therapy and needle and syringe programs.[3]

Health systems with a wide range of epidemiologic scenarios can benefit from targeting PWID for micro-elimination. It is believed that with expanded screening for HCV, especially among PWID, Iceland could reach the WHO targets by 2020, becoming one of the first countries to achieve HCV elimination.[2] The government of Iceland committed to a comprehensive elimination program despite the fact that the country's estimated HCV-infected population in 2014 was only 1100.[80] At the other end of the spectrum, Georgia, a country with one of the highest global burdens of HCV, has developed an elimination pilot

program that includes intensified HCV detection efforts and increased harm reduction services for PWID.[3 4] In the UK, the Tayside region of Scotland is being used as a test bed of regional micro-elimination, using an integrated combination of pathways to target all groups infected with HCV, especially focusing on treatment of PWID in needle exchange programs, to prove the concept of "treatment as prevention." The complementary pathways to needle exchange include: conventional nurse-led outreach programs, pharmacist-led treatment of patients on opioid substitution therapy in community pharmacies, treatment in prisons, and treatment by embedded hepatitis specialist nurses in addiction treatment centers. All of these services will deliver the volume of treatment modeled to reduce prevalence below 10% and incidence to below 1% over 3 years, thereby achieving elimination.[3]

People with hemophilia and other inherited blood disorders

Prior to 1990, transfusion of blood and blood products was the primary vector for transmission of HCV infection in people with hemophilia and other hereditary blood disorders, such as Von Willebrand disease and thalassemia. [3] The burden of HCV disease remains high in this population, even in high-income countries where there have been almost no new cases of HCV in patients with hemophilia in recent years. Those with hemophilia have much higher mortality due to chronic HCV than the general public.[86] In the past, these patients often declined HCV treatment due to side-effects, but DAAs are much better tolerated and are highly effective in this population. A Japanese study investigated the safety and efficacy of DAAs among 27 individuals with hemophilia and HCV/HIV coinfection. All study patients achieved SVR after receiving interferon-free DAA therapy.[3] Walsh et al. found similar results in a study that enrolled individuals with chronic HCV and inherited blood disorders (hemophilia and Von Willebrand disease) in the United States.[3] Patients with thalassemia have also responded well to DAA treatment, with high SVR rates and few side-effects, even those who had not responded to previous interferon treatment and were considered difficult to treat.[3 4] These studies suggest that individuals with inherited blood disorders may safely and successfully be treated for HCV with DAA therapy.[88] Ireland's elimination of HCV in patients with hemophilia[3] (Box 3) and Slovenia's in patients with all congenital bleeding disorders[4] suggest that the lack of new infections and effectiveness of DAA treatment make micro-elimination in these groups of patients highly achievable.

Prisoners

Prisoners in most countries have a higher prevalence of HCV than the general population, but their access to treatment is very limited. [2 4] Although this high prevalence is in part due to conditions and experience prior to incarceration, with drug use, tattooing, and sexual activity being high-risk factors, once in prison, stresses including overcrowding and violence can cause inmates to begin or continue unsafe activities, resulting in a 30% estimated rate of new infections annually.[93] Barriers to treatment include lack of testing, social stigma, and lack of availability of treatment options. HCV interventions, including treatment, can be delivered safely and effectively in prison settings, and should be an essential component of any national elimination strategy.[4 5] Treatment within prisons has been shown to be cost effective in Scotland, even at DAA costs that are now historical.[4]

A rapid DAA scale-up program initiated at a correctional facility in Cairns, Australia as part of a larger elimination strategy resulted in a fall in the prevalence of HCV viremia within the

prison from approximately 12% to <1% over a 22-month period, thereby effectively achieving HCV micro-elimination in this institution.[4] Six reinfections were seen in the population studied, which underscores that incident cases of HCV will continue to occur unless serious efforts are made to improve harm reduction services in prisons.[4 5] Nurse-led and specialist-supported models of care in Australian correctional facilities have been demonstrably effective in increasing treatment uptake among inmates with chronic HCV, with treatment responses in excess of 95% in some facilities.[4 5] A study in Spain reported similar results, with a >99% adherence rate and a prevalence drop from 9.9% to .5% over the year it ran. All treated inmates achieved SVR after 8 or 12 weeks of treatment.[4] Notably, this study also created a sustainable model for continuance: even after its completion, all new prisoners are screened and offered treatment.[4] Rapid HCV testing and DAA treatment can also feasibly be delivered in transient jail populations, where inmates are often detained for fairly short or unpredictable periods of time, as observed by two studies conducted in the United States.[95 5] In many countries, however, it is common for remand prisoners to be incarcerated for one week or less. Initiatives that target remand prisoners for HCV testing and treatment should have a strong linkage-to-care component with mechanisms for transferring care from the prison setting to the community setting upon release.

Transplant recipients

HCV infection increases mortality and graft loss in transplant recipients[53 55 4],making them an important target group for a micro-elimination approach. In the past, HCV treatment post-transplant was fraught with poor tolerance and was often unsuccessful. New DAA treatments have proven to be both safe and effective, and all transplant recipients who are viremic for HCV should be offered treatment before or after transplant.[58] Therefore, the question in transplant recipients is less a matter of whether to treat HCV but when to do so. The majority of transplant recipients should be treated prior to surgery, but in a small subset of patients whose liver disease is so advanced that pre-transplant DAA therapy is either unsafe or ineffective, treatment should be delayed until after surgery.[4] There are increasingly calls to consider using HCV-positive organs in HCV-negative recipients[4 5], but this practice should be implemented only in the context of timely access to DAA therapy.

Conclusion

The micro-elimination approach discussed in this article has the potential to catalyze progress against HCV in a diverse range of epidemiologic settings. Stakeholders pursuing HCV elimination targets in countries worldwide should work together to further develop a micro-elimination agenda that will enhance these efforts. Such an agenda should call for rigorous research including social science research to document the outcomes of micro-elimination initiatives. The monitoring of micro-elimination outcomes should incorporate key indicators of progress toward the WHO HCV elimination targets. WHO's proposed viral hepatitis monitoring framework contains several indicators that are relevant for HCV micro-elimination initiatives, including the following: (1) prevalence of HCV infection; (2) people living with HCV diagnosed; (3) treatment initiation; (4) cure; and (5) deaths from hepatocellular carcinoma, cirrhosis and liver diseases attributable to HCV.[4] It is advisable to draw from the WHO indicators as much as possible in developing monitoring frameworks for micro-elimintation initiatives, as this will facilitate comparisons of outcomes and will allow for the aggregation of data across different settings.

Research and stakeholder consultation are needed to develop decision-making tools for health systems that are exploring how to make the most strategic use of the micro-elimination approach. A number of candidate micro-elimination populations are relatively easy to reach because they are already patients in care, e.g., for kidney disease, HIV or opioid substitution therapy. However, these populations do not necessarily include the largest numbers of HCV-infected people or the ones at greatest risk of transmitting the disease to others. A much greater expenditure of resources may be required to reach HCV-infected people who are not already in care – but the return on the investment could potentially be greater strides toward elimination. Navigating decisions of this nature will require a much better evidence base than what is currently available. The publication of real–world operational research findings will greatly advance the micro-elimination agenda in the coming years, and will aid stakeholders in combining different micro-elimination models to achieve full-scale elimination and reach the 2030 HCV elimination targets.

BOX 1 – What about MACRO-elimination?

While the micro-elimination approach may be appealing to countries that are not yet prepared to fully implement national HCV elimination plans, it also speaks to the needs of countries pursuing full-scale elimination in that it emphases the importance of providing tailored services to reach specific populations whose engagement will be essential for achieving elimination. Although the launch of Iceland's national HCV elimination program predates the introduction of the micro-elimination concept, it provides an instructive example of how the micro-elimination approach can enhance broader initiatives.

A small nation of 340,000 people, all covered by national health insurance, Iceland had an estimated viraemic HCV population of 1,100 in 2014, with most cases resulting from injecting drug use. In 2015, Gilead Sciences and the relevant Icelandic parties came to an agreement that Gilead would provide DAAs to all of these patients and Iceland would provide the organization, diagnostic tests, and other related services required for the nationwide elimination campaign. An observational study would provide 36 months of treatment followed by 15 years of long-term follow-up observation.

The idea is that by treating all patients in Iceland within a short timeframe and also providing other harm-reduction measures such as needle exchange services and opioid substitution therapy, there would consequently be fewer new infections, allowing for total elimination of the disease and proving the concept of "treatment as prevention." All patients are offered testing and treatment regardless of whether they agree to participate in the study's research arm. Active outreach and travel assistance are offered to encourage patients to take advantage of the program. The majority of patients were treated in the first two years, with the third year being devoted to new diagnoses and catching those cases that fell through the cracks, including relapses and reinfections. Long-term monitoring will track the incidence of domestic transmission as well as any long-term complications. It is expected that this aggressive, multi-pronged initiative will result in Iceland eliminating HCV well ahead of the WHO timeline as well as providing evidence that will aid other countries pursuing

elimination goals.[80] In the first 15 months of the program, 554 people with HCV were evaluated, of whom 94% initiated treatment. Viremic HCV prevalence among PWID dropped from 43% at baseline to 12% in 2017, a 72% reduction.[4]

BOX 2 – Children and HCV

Estimates of prevalence of HCV in children and adolescents range from .05%–.36% in high-income countries to 1.8%–5.8% in some heavily affected low-income countries, but it is likely that these data severely underestimate actual prevalence.[4] There are notable differences in how HCV manifests in children and adults, including progression of liver damage, clearance rates, treatment options, and length of potential chronic infection.[4] Most infection in children is due to vertical transmission, but injecting drug use is an increasingly common infection route, especially for adolescents.[4] Liver disease in children with chronic HCV is usually minor and there is often little evidence of progression.[4] Although progression from fibrosis to cirrhosis is rare, occurring in approximately 2–3% of cases, fibrosis does progress: nearly a third of the 44 children with multiple liver biopsies (6 years apart on average) in the PEDS-C trial had increased severity of fibrosis, and the proportion with cirrhosis or bridging fibrosis increased from 11% to 20%.[113] Spontaneous clearance rates are slightly higher for children than adults, mostly among children infected via vertical transmission, who have a 25–40% chance of spontaneous viral clearance.[43] Treatment for children with HCV is significantly behind that of their adult counterparts. Only in early 2017 were the first DAA treatments approved for adolescents (aged 12–17 years), and although studies on younger children are underway, currently the only treatments available for them are interferon-based, which tend to be less effective and more toxic.[5 112] Because of the side-effects of interferon-based treatments and the generally slow progression of liver disease in children, as well as the expectation of increasing availability of DAAs for children, treatment is not currently advised for children under 12 years in most cases.[5 112]

BOX 3 – Eliminating HCV in people with hemophilia: the Irish experience

Ireland implemented a strategy with elements of the micro-elimination approach in its elimination of HCV in people with hemophilia. In 1999–2001, Ireland held a tribunal inquiring into HCV and HIV in hemophiliacs and others who were infected via blood and blood products provided by the State. Its findings led the tribunal to call for the creation of a coordinating committee focusing on the care and treatment of patients with hemophilia, as well as for better communication among doctors caring for patients with hemophilia.[4] In response, stakeholders formed the National Haemophilia Council, an advisory board consisting of a wide range of public health officials, advocacy groups, and medical professionals. When DAAs became available, the National Haemophilia Council and other groups advocated strongly for them to be offered to patients with hemophilia. The Department of Health consequently assured the Council that all State-infected patients would receive treatment beginning in mid-2015. This goal was met, and at the end of 2016 it was announced that hepatitis C had been eliminated among patients with hemophilia in Ireland.[4] Although Ireland was successful, a true micro-elimination approach would include more specific quantitative goals and more detailed reporting of plans, progress and outcomes in order to make the process fully transparent. A notable lesson to take away from the Irish experience is that a history of effective multi-stakeholder collaboration in response

to the health needs of some HCV-affected populations may provide a good foundation for a micro-elimination initiative. Ireland now has a hepatitis elimination plan for the country, with 2026 as the target year.[4] The program is supported by a Clinical Advisory Group made up of health care professionals involved in the delivery of care to patients with HCV across a number of disciplines.

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