



# The successful scale-up of direct-acting antiviral hepatitis C treatments will benefit from concerted investments in implementation science

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## Abstract

The introduction of highly efficacious direct-acting antiviral (DAA) treatment therapeutics presents new opportunities to both directly reduce chronic hepatitis C virus (HCV) prevalence and prevent the onward transmission of HCV. To achieve the equitable scale-up of DAA interventions at the population level, however, reductions in HCV incidence and prevalence must be achieved among entire populations of people living with HCV—all in “real-world” conditions. In this commentary, we describe five problem areas that will benefit from new investments in implementation science in order to inform the scale-up of DAA interventions: (1) New evidence is needed to optimize the integration of DAA treatments into generalist models of care; (2) DAA scale-up needs to be adaptive to the needs of highly diverse and large populations living with HCV who will benefit from DAA interventions; (3) we need to do better at measuring and responding to features of implementation context; (4) costs need to be explicitly assessed in “real time”; and (5) new research-community-practice partnerships are needed to inform evolving HCV testing, treatment and prevention guidelines, policies, and programs. We offer solutions to address these problem areas, with an emphasis on describing how investments in implementation science can address each of these challenges “head on.”

## Résumé

L'introduction des traitements thérapeutiques très efficaces d'antiviraux à action directe (AAD) présente de nouvelles opportunités pour réduire directement la prévalence chronique du virus de l'hépatite C (VHC) et pour prévenir la transmission ultérieure du VHC. Cependant, afin d'atteindre une mise à l'échelle équitable des interventions d'AAD au niveau de la population, des réductions de l'incidence et de la prévalence du VHC sont nécessaires au sein de la population entière des personnes vivant avec le VHC et ce, en tenant compte des conditions réelles. Dans ce commentaire, nous décrivons cinq problématiques qui bénéficieront de nouveaux investissements en science de la mise en œuvre pour informer la mise à l'échelle des interventions d'AAD : (1) De nouvelles données scientifiques sont nécessaires pour optimiser l'intégration des traitements de AAD dans les modèles de soins généralistes; (2) La mise en place à grande échelle doit être adaptée aux besoins des diverses populations qui vivent avec le VHC et qui bénéficieront des interventions d'AAD; (3) Nous devons améliorer nos mesures et nos interventions dans le contexte de la mise en œuvre; (4) Les coûts doivent être évalués de façon explicite et en temps réel; et (5) De nouveaux partenariats entre les chercheurs, la communauté et les professionnels de la santé sont nécessaires pour informer le dépistage, les directives de traitement et prévention du VHC, les politiques et les programmes. Nous proposons des solutions pour répondre aux problèmes soulignés, en mettant l'accent sur la façon par laquelle les investissements en science de la mise en œuvre peuvent adresser chaque défi.

**Keywords** Hepatitis C · Implementation science · Scale-up · Treatment

**Mots-clés** Hépatite C · Science de la mise en œuvre · Mise à l'échelle · Traitement

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The introduction of highly efficacious direct-acting antiviral (DAA) treatment therapeutics presents new opportunities to both directly reduce chronic hepatitis C virus (HCV) prevalence (Martin et al. 2013) and prevent the onward transmission of HCV (Pearlman and Traub 2011). To achieve the

equitable scale-up of DAA interventions at the population level, however, reductions in HCV incidence and prevalence must be achieved among entire populations of people living with HCV (Pearlman and Traub 2011). To date, however, the vast majority of research regarding DAA has taken place within controlled settings (e.g., clinical trials), with less attention devoted to the translation of DAA treatment practices and policies into health systems and service delivery practices. It remains unclear how individual factors (e.g., attitudes towards HCV care; HCV risk behaviour) may interact with social-structural conditions (e.g., health care service delivery systems) to influence the scalability (e.g., rate of uptake; equitable reach) and sustainability (e.g., preventing reinfections; short- and long-term impacts on limited resources) of enhanced DAA intervention efforts. Below, we describe five problem areas that will benefit from new investments in implementation science in order to inform the scale-up of DAA interventions.

### **Problem 1: New evidence is needed to optimize the integration of DAA treatments into generalist models of care**

With a growing shortage of specialists available to meet the increasing demand of patients eligible for initiating DAA treatment, combined with a far more simplistic treatment regimen (e.g., minimal side effects; high clearance rates; short regimens), health systems worldwide are presented with a critical opportunity to integrate HCV treatment into generalist models of care. Consider, for example, how HCV treatment no longer requires the care and oversight of a hepatologist. Promisingly, for example, emerging evidence indicates that decentralizing HCV treatment services to primary care (e.g., among primary care practitioners and nurse practitioners) attains similar patient outcomes as compared to approaches that centralize HCV care within specialist models (Kattakuzhy et al. 2017). Indeed, lessons can be learned from early adopter settings such as Australia where non-specialists are now prescribing almost half of DAA treatment initiations (Scott et al. 2018).

Investments in research dedicated to addressing implementation challenges associated with expanding the scope of practice of DAA treatment to new prescribers represents a key area that will benefit from concerted investments in implementation science. We suggest that close study and evaluation of generalist-prescriber models of care are needed to better understand how this decentralization impacts various features of the health care service delivery systems, including resource impacts. For example, by drawing on frameworks of implementation science that seek to identify and adapt causal implementation factors (e.g., patient, provider, organizational, and structural factors) and outcome measures (e.g., adoption, fidelity, costs, penetration, sustainability), policy makers and

other stakeholders can identify the key actionable implementation decisions available to optimize the integration of HCV care into generalist models of care (Chaudoir et al. 2013).

### **Problem 2: DAA scale-up needs to be adaptive to the needs of highly diverse and large populations living with HCV that will benefit from DAA interventions**

To date, only a small proportion—approximately 13%—of people living with HCV (approximately 71 million people worldwide have chronic HCV infection) have received DAA treatment (World Health Organization 2018). There is growing concern that the successes in this area have been largely achieved among the proverbial “low-hanging fruit”—i.e., the easiest to “reach” populations (van Santen et al. 2017). The growing number of eligible patients is comprised of a highly diverse set of populations, and the social and structural forces that conventionally impede the engagement of populations living with HCV with public health programs make implementation challenges particularly salient in relation to the treatment and prevention imperatives of DAA interventions for vulnerable populations. For example, gay, bisexual, and other men who have sex with men, people living in prisons, and people who inject drugs living with HCV likely require very different treatment trajectories (e.g., health system and social supports, treatment initiation opportunities) than other populations, including “baby boomers.”

We suggest that achieving success with DAA at the population level faces a set of complex implementation challenges that will benefit from social scientific approaches to implementation science that emphasize how pharmacotherapy interventions (i.e., DAAs) are also inherently *social* interventions. For example, we argue the importance of recognizing the extent to which the effective scale-up of DAA treatments will require the mobilization of large and diverse populations of people living with HCV to engage with the various facets of the HCV cascade of care (Bird et al. 2018). As DAA interventions are being scaled up within and across jurisdictions, new empirical approaches are needed to identify, collect, monitor, and respond to “feedback” (i.e., adapt) in ways that enhance the capacity to meet the needs of diverse populations, with a particular emphasis on providing opportunities for treatment among populations that are “hidden” or potentially vulnerable.

### **Problem 3: We need to do better at measuring and responding to features of implementation context**

As we have argued elsewhere, context is an important rubric through which to study the processes of intervention

implementation (Shoveller et al. 2016). We suggest that there is a need to better understand how features of implementation context influence the scalability (e.g., equitable reach, rate, and pace of uptake) of HCV screening, treatment initiation, and long-term prevention practices among people living with HCV in a post-DAA era. For example, better understandings of context (e.g., the social and structural conditions in which an intervention occurs) can provide key insights into how intervention outcomes in “real-world” conditions have differential effects—including equity- or inequity-enhancing effects—within and across various health systems and among key populations (Shoveller et al. 2016).

The intensive study of the adaptation and scale-up of DAA interventions needs to be done in ways that concomitantly consider the broader implementation context, and advancing this area of science will benefit from methods, theory, and frameworks from implementation science. For example, the Consolidated Framework for Intervention Research (CFIR) (Damschroder and Lowery 2013) is an example of an implementation science framework that can be used to inform how interventions should be adjusted and refined to optimize both process and outcome measures. Further, CFIR also provides theory-based constructs for developing logic models, generalizable theory, and, ultimately, context-sensitive implementation decisions to optimize intervention decisions and outcomes.

#### **Problem 4: Costs need to be explicitly assessed in “real time”**

We need to develop “real time” understandings about cost implications, including with regard to cost-effectiveness and cost-benefits. Because DAAs need to be delivered in health settings of varying complexity and overheads, the overall costs of scaling up DAAs may vary as they go to scale (Proctor et al. 2011). “Real time” analyses of cost-related data will provide administrators and decision-makers with key insights into the feasibility (e.g., in settings that are poised to scale up DAAs), penetration (e.g., varying costs by setting/population), and sustainability (e.g., capacity to maintain scaled-up approaches over the medium to long term) of DAA interventions in order to optimize implementation strategies while minimizing extraneous costs.

#### **Problem 5: New research-community-practice partnerships are needed to inform evolving HCV testing, treatment and prevention guidelines, policies, and programs**

The HCV cascade of care is rapidly evolving, thereby underscoring the importance of implementing partnerships

that are “nimble” and can provide evidence-informed adaptations to clinical care and policy that are both context-sensitive and population-specific. The ontological praxis of those working in this area needs to be founded upon effective community-based partnerships and institutionalized support mechanisms that can be directly integrated within ongoing education and training initiatives for health and other professionals, as well as the direct involvement with developing and disseminating evidence-based clinical practice guidance and program standards. This approach directly embeds the decision-making at a research-policy interface that is community-informed, thereby maximizing the potential to contribute to *systems-level* change in ways that can respond to the realities of health systems, challenges faced by service providers, and the needs of various communities affected by HCV.

Drawing on and combining principles from community-based research (e.g., mitigation of power differentials) with key principles of team science (e.g., high-quality communication) can provide opportunities to establish governance structures to guide and sustain research and planning/practice collaborations for interdisciplinary teams to work together—a critical element in our attempt to “fill” the science-program paradigm gap (Blanchard and Aral 2010). Through the development of effective research-community-practice partnerships, we will also better have the capacity to combine insights derived from data sets collected within and across various contexts and populations. These efforts will also benefit from international collaborations, which will bring into sharper focus the pooled effects of how features of implementation context, health care delivery systems, and individual behaviour impact the outcomes of ongoing and future DAA interventions. For example, it can become highly feasible to learn from the outcomes of “others,” including the successes made in settings where DAAs have been implemented, aggressively scaled up, as well as provide critical opportunities to implement readiness and acceptability research in settings that are poised to make DAA available in the future.

#### **Investments in implementation science can address each of these problems “head on”**

While DAAs represent a “game changer” for people living with HCV, population-level benefits can only be achieved via the enhancement of HCV case-finding efforts, timely and widespread uptake of DAA immediately following HCV diagnoses, and high proportions of HCV-viremic individuals attaining a sustained virologic response and avoiding reinfection over the long term. The intensive study of the implementation factors that influence success with each facet of the HCV cascade of care, with a context-sensitive approach and an eye to the experiences of key populations who have historically experienced social and structural impediments to HCV

care (e.g., people who inject drugs, and gay, bisexual, and other MSM), are urgently needed to ensure equitable access to DAA treatment for all. Now is the time to generate new investments in implementation science that will provide opportunities to guide the rapid-cycle evaluation of the implementation of the evolving HCV cascade of care as it provides a comprehensive framework for systematically identifying the implementation factors that may emerge as a host of nations scale up DAA interventions.

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## References

- Bird, K., Socías, M. E., & Ti, L. (2018). Integrating hepatitis C and addiction care for people who inject drugs in the era of direct-acting antiviral therapy. *The International Journal on Drug Policy*, *59*, 1–2.
- Blanchard, J. F., & Aral, S. O. (2010). Program science: an initiative to improve the planning, implementation and evaluation of HIV/sexually transmitted infection prevention programmes. *The Medical Society for the Study of Venereal Disease*.
- Chaudoir, S. R., Dugan, A. G., & Barr, C. H. (2013). Measuring factors affecting implementation of health innovations: a systematic review of structural, organizational, provider, patient, and innovation level measures. *Implementation Science*, *8*(1), 22.
- Damschroder, L. J., & Lowery, J. C. (2013). Evaluation of a large-scale weight management program using the consolidated framework for implementation research (CFIR). *Implementation Science*, *8*, 51.
- Kattakuzhy, S., Gross, C., Emmanuel, B., Teferi, G., Jenkins, V., Silk, R., et al. (2017). Expansion of treatment for hepatitis C virus infection by task shifting to community-based nonspecialist providers: a nonrandomized clinical trial. *Annals of Internal Medicine*, *167*(5), 311–318.
- Martin, N. K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S. J., Lima, V. D., et al. (2013). Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*, *58*(5), 1598–1609.
- Pearlman, B. L., & Traub, N. (2011). Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clinical Infectious Diseases*, *52*(7), 889–900.
- Proctor, E., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunker, A., et al. (2011). Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Administration and Policy in Mental Health and Mental Health Services Research*, *38*(2), 65–76.
- Scott, N., Hainsworth, S. W., Sacks-Davis, R., Pedrana, A., Doyle, J., Wade, A., et al. (2018). Heterogeneity in hepatitis C treatment prescribing and uptake in Australia: a geospatial analysis of a year of unrestricted treatment access. *Journal of Virus Eradication* *4*(2), 108.
- Shoveller, J., Viehbeck, S., Di Ruggiero, E., Greyson, D., Thomson, K., & Knight, R. (2016). A critical examination of representations of context within research on population health interventions. *Critical Public Health*, *26*(5), 487–500.
- van Santen, D. K., van der Helm, J. J., Lindenburg, K., van der Loeff, M. S., & Prins, M. (2017). HIV and hepatitis C treatment uptake among people who use drugs participating in the Amsterdam Cohort Studies, 1985–2015. *The International Journal on Drug Policy*, *47*, 95–101.
- World Health Organization. Hepatitis C. 2018.