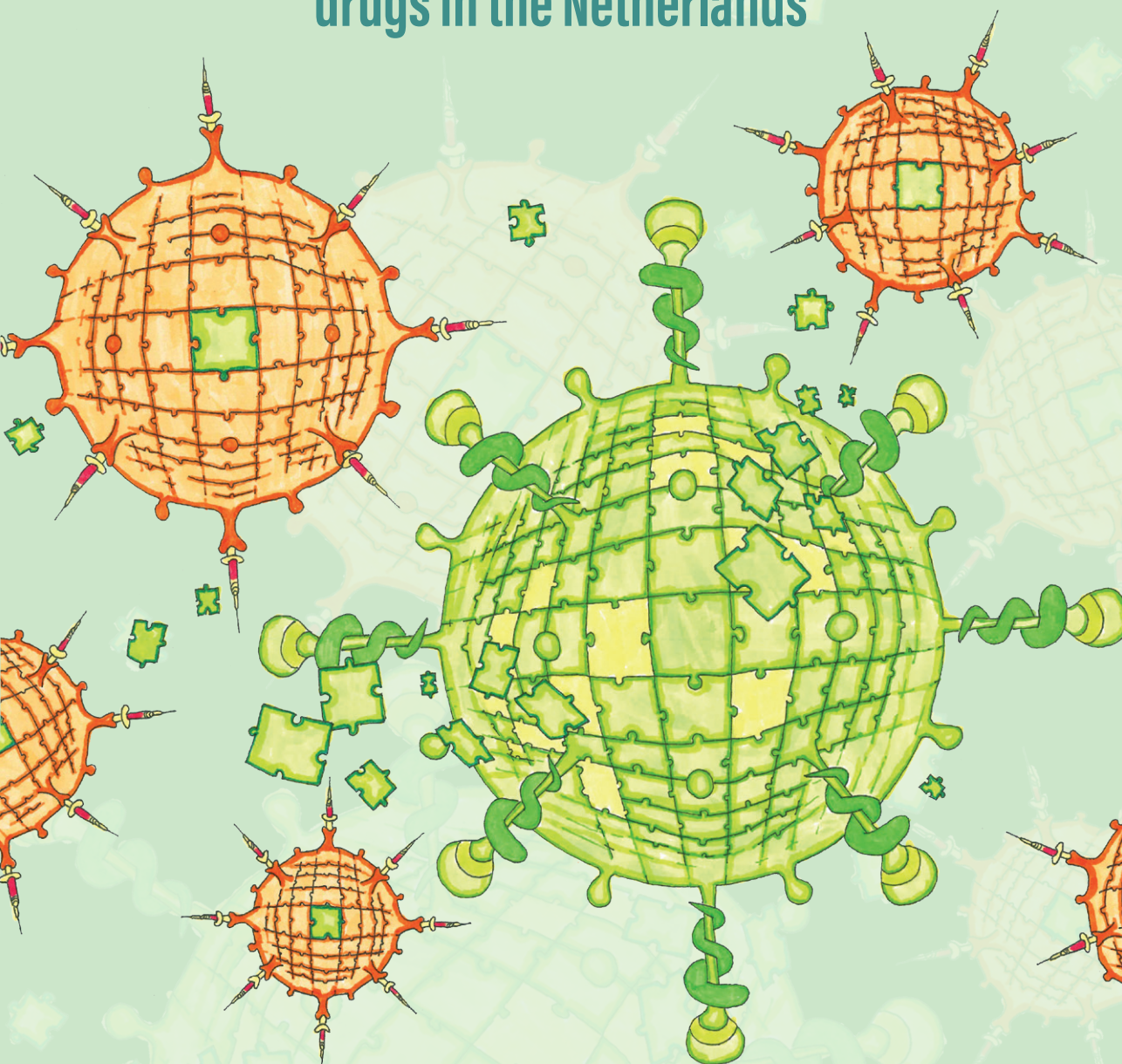


Towards hepatitis C elimination through decentralized care for people who use drugs in the Netherlands



Daan W. Von den Hoff

**RADBOD
UNIVERSITY
PRESS**

Radboud
Dissertation
Series

Towards hepatitis C elimination through decentralized care for people who use drugs in the Netherlands

Daan Von den Hoff

This publication has been made possible by



Towards hepatitis C elimination through decentralized care for people who use drugs in the Netherlands

Daan Von den Hoff

Radboud Dissertation Series

ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS

Postbus 9100, 6500 HA Nijmegen, The Netherlands

www.radbouduniversitypress.nl

Design: Proefschrift AIO | Annelies Lips

Cover: Myrthe van den Heuvel and Guntra Laivacuma

Printing: DPN Rikken/Pumbo

ISBN: 9789465152899

DOI: 10.54195/9789465152899

Free download at: <https://doi.org/10.54195/9789465152899>

© 2026 Daan Von den Hoff

**RADBOUD
UNIVERSITY
PRESS**

This is an Open Access book published under the terms of Creative Commons Attribution-Noncommercial-NoDerivatives International license (CC BY-NC-ND 4.0). This license allows reusers to copy and distribute the material in any medium or format in unadapted form only, for noncommercial purposes only, and only so long as attribution is given to the creator, see <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Towards hepatitis C elimination through decentralized care for people who use drugs in the Netherlands

Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

maandag 24 augustus 2026
om 14.30 uur precies

door

Daan Willem Von den Hoff
geboren op 27 december 1993
te Almere

Promotoren:

Prof. dr. J.P.H. Drenth

Prof. dr. A.F.A. Schellekens

Copromotor:

Dr. F.A.C. Berden

Manuscriptcommissie:

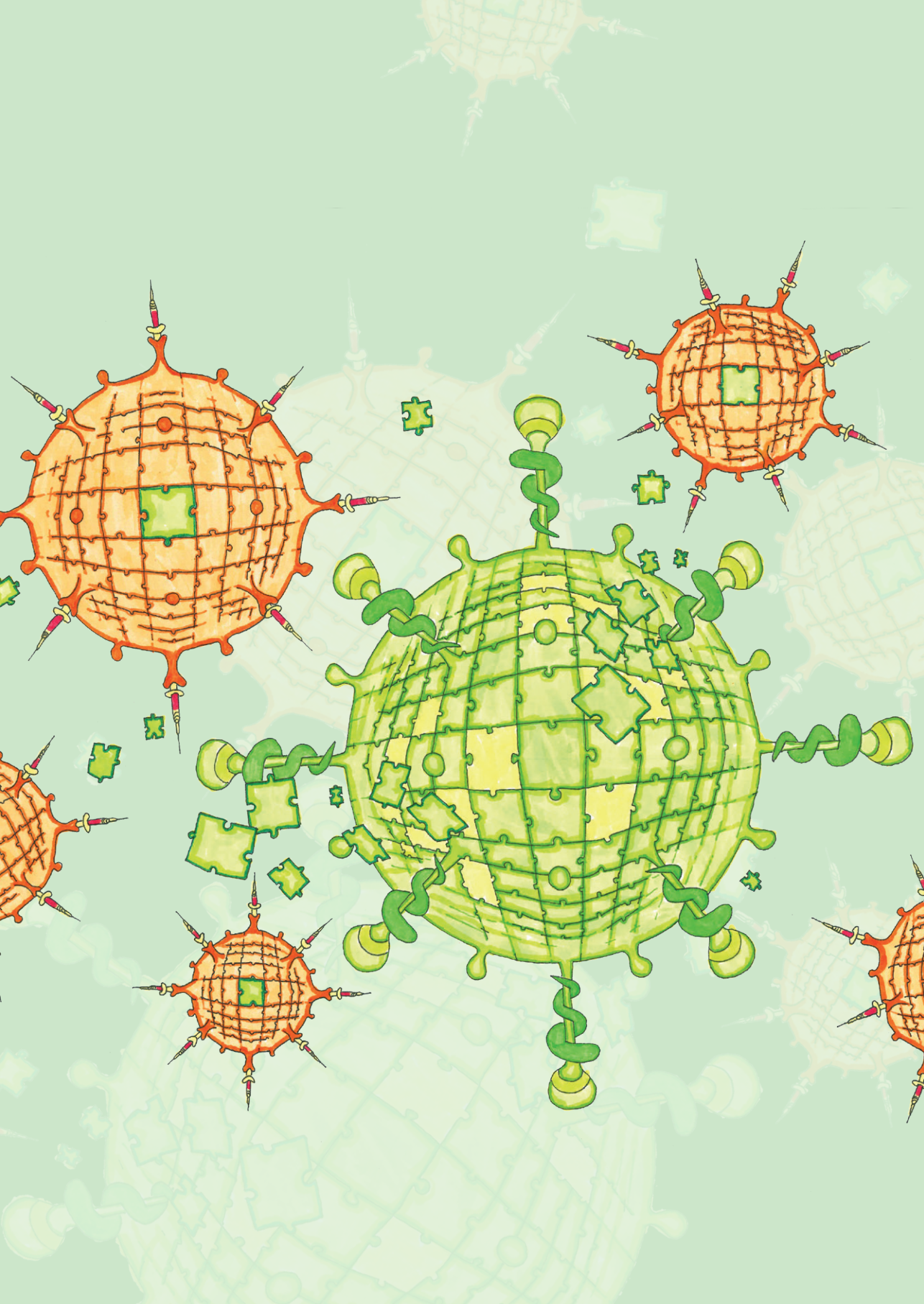
Prof. dr. R.B. Kool

Prof. dr. M. van der Valk (Amsterdam UMC)

Dr. B.A.G. Dijkstra

Table of Contents

Chapter 1.	General Introduction	7
Part 1: Addiction and hepatitis C, two interacting conditions		
Chapter 2.	Against All Odds? Addiction History Associated with Better Viral Hepatitis Care: A Dutch Nationwide Claims Data Study	19
Chapter 3.	The impact of Hepatitis C Cure on Methadone Pharmacokinetics: A Case Series	39
Part 2: Implementing decentralized hepatitis C care in Dutch addiction care		
Chapter 4.	Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care. Study protocol for the Hepatitis C: chain of addiction care (CAC) project	55
Chapter 5.	Successful hepatitis C elimination through decentralized treatment in Dutch addiction care: a RE-AIM based evaluation	69
Chapter 6.	Facilitators and barriers for implementation of a decentralized hepatitis C care chain for people who use drugs in Dutch addiction care	87
Chapter 7.	General Discussion	107
Chapter 8.	Appendices	
	Summary	121
	Summary in Dutch	123
	About the author	126
	List of Publications	128
	Research data management	130
	PhD Portfolio	132
	Acknowledgments	134



Chapter 1

General Introduction

Adapted from: Hepatitis C-virus behandeling met direct-werkende antivirale middelen in de verslavingszorg. *Von den Hoff, D.W., Berden, F.A.C., Smolders, E. Published in Psyfar 01 February 2022.*

If the mountain won't come to Mohammed, then Mohammed must go to the mountain:
Decentralization of hepatitis C care for people who use drugs. *Daan W. Von den Hoff, Floor A. C. Berden, Arnt F. A. Schellekens; Published in United European Gastroenterology Journal 22 October 2021*

Hepatitis C

Pathophysiology and management

Hepatitis C virus (HCV) is a single-stranded RNA virus. The virus infects hepatocytes and causes hepatitis. Transmission of HCV primarily occurs through blood-to-blood contact, such as through transfusions, medical procedures, tattooing or injecting drug use with contaminated needles. Sexual transmission plays a minor role. HCV exhibits high genetic variability, with at least seven major genotypes and numerous subtypes. An acute hepatitis C infection is clinically apparent in fewer than 25% of patients and is rarely fulminant (<1%). Following this acute phase, approximately 80% of individuals develop a chronic infection, while the remaining 20% achieve spontaneous viral clearance (Figure 1). The chronic phase is typically asymptomatic (1). However, chronic hepatitis C infection leads to progressive hepatic fibrosis, resulting in liver cirrhosis in approximately 10–20% of patients after 20 to 30 years (2). Among patients who develop cirrhosis due to chronic HCV, 10–20% may experience complications, including hepatocellular carcinoma and decompensated cirrhosis (e.g., ascites, hepatic encephalopathy, and esophageal varices with risk of bleeding). For this reason, people with cirrhosis remain under specialist care, typically by a hepatologist (1, 2).

The introduction of direct-acting antiviral (DAA) therapy in 2014 has drastically transformed the global treatment landscape for HCV. Previously, treatment consisted of long-term (pegylated) interferon and ribavirin. This combination therapy yielded a sustained virologic response (SVR) rate of 40–80% dependent on genotype (3). These are relatively low response rates, particularly considering the significant side effects experienced by a substantial proportion of patients. In contrast, current treatment with pangenotypic DAAs, such as glecaprevir/pibrentasvir or sofosbuvir/velpatasvir, results in SVR rates exceeding 95% after 8 or 12 weeks of therapy, regardless of viral genotype. These agents have mild adverse events and limited contraindications. After widespread DAA availability, the World Health Organization (WHO) set ambitious global targets for eradication of hepatitis C by 2030, a reduction in new infections by 90%, and a reduction in mortality by 65% (4). To achieve these goals, elimination efforts increasingly focus on populations with a high prevalence of infection, where the largest population-level impact can be achieved.

Hepatitis C in people who use(d) drugs

The worldwide prevalence of chronic HCV is around 1.0% (5). In most Western countries the prevalence is lower, and in the Netherlands it is estimated to be

around 0.3% (6). The WHO elimination strategy focuses on specific populations where the prevalence rates are higher, in particular people who use(d) drugs (PWUD) (6, 7). In the Netherlands prevalence rates for HCV among people who inject(ed) drugs were estimated up to 59% in 2019 (6). Prevention and treatment of this population are crucial to reach WHO goals (8). Prevention strategies to reduce (re)infection include screening of blood products, safe injection practices, needle exchange programs, and opioid agonist therapy to prevent injecting drug use (e.g., methadone or buprenorphine) (9). In the Netherlands, these interventions have been well implemented, resulting in a negligible number of new infections (10, 11).

Treatment of HCV can be considered secondary prevention, as it reduces the population-level prevalence and thereby limits ongoing transmission. DAAs are particularly well-suited for treating the PWUD population due to their efficacy, safety and ease of use. Simplified treatment regimens have also been included in international guidelines to support use in non-expert settings, such as addiction care where PWUD are most readily reached (2, 12). In the Netherlands, addiction care is provided by regional addiction care centers across the country and is largely covered by mandatory health insurance. As a result, addiction care is widely available, reimbursed and accessible to everyone through referral from primary care (general practitioners). Addiction care centers offer prevention, multidisciplinary addiction treatment and harm reduction services, provided by doctors, nurses, psychologists and other staff. Addiction care plays a pivotal role in supporting PWUD and promoting public health (13). Therefore, addiction care could play a crucial part in managing HCV and be a driving force behind its elimination.

Challenges in the management of hepatitis C in people who use(d) drugs

Complex interplay between addiction and HCV (part one of this thesis)

While the biomedical understanding of HCV and its treatment have advanced significantly, healthcare systems have struggled to effectively reach PWUD. This might be because the two conditions negatively influence each other on transmission, as well as disease progression, barriers to care, and treatment interactions. The interplay begins with HCV transmission routes, making PWUD directly vulnerable through shared needles. However, substance use is also linked to incarceration, homelessness, and unsafe sexual practices (14). The burden of disease is also higher in PWUD due to accelerated *fibrosis progression* in the presence of additional hepatic stress, such as from excessive alcohol use, metabolic

factors (including hypertension, obesity, and hypercholesterolemia), or co-infection with hepatitis B virus or Human Immunodeficiency Virus (HIV); all of which are more prevalent in this population (1).

When HCV treatment is considered, barriers to optimal care may present themselves. PWUD can face stigma and negative attitudes from healthcare providers, which could lead to suboptimal care or deter them from engaging with HCV care (15). A review by van Dijk and colleagues studying loss to follow up in people who inject drugs found that only a median of 50% of PWUD diagnosed with HCV consult with an HCV specialist, and just 53% of those initiate treatment (16). Literature further suggests that for PWUD, accessing HCV outpatient specialty care can be challenging, possibly as a result of financial constraints, limited capacity to travel, and low trust in healthcare providers (17). These factors have been studied extensively internationally, however it remains unclear whether these result in suboptimal hospital HCV care in the Netherlands, where HCV care as well as addiction care is insured and travel distance to the hospital is generally low.

When treatment with pangenotypic DAAs is initiated in PWUD, there are a few relevant interactions with medication used in addiction care. For instance, the DAA combination glecaprevir/pibrentasvir is a weak inhibitor of CYP3A4 and CYP1A2 and causes modest increases in exposure of substrates such as midazolam and caffeine, which are generally considered not clinically relevant. Nevertheless, for certain psychotropic drugs metabolized via these pathways (e.g. aripiprazole, lurasidone, and clozapine), a slight increase in drug exposure may occur. Additionally, both glecaprevir/pibrentasvir and velpatasvir/sofosbuvir inhibit drug transporters, particularly P-glycoprotein, which may further increase exposure to P-glycoprotein substrates such as quetiapine, risperidone, and lurasidone, especially at higher doses. Lastly, PWUD at risk for HCV often require long-term opioid agonist treatment to counteract withdrawal and mitigate substance use related problems. About 33% of people with opioid-related problems within Dutch addiction care is using methadone for this indication (11). Although DAAs have no significant drug-drug interactions with methadone, HCV treatment might have an effect on drug metabolism and consequently on methadone plasma levels (18). Methadone's efficacy and safety depend on maintaining appropriate plasma levels, which are influenced by the CYP enzyme system, particularly CYP3A4. HCV infection might influence this process, and when HCV is eliminated it might restore CYP3A4 function. This subject has not been studied *in vivo*, but may be relevant as it potentially affects withdrawal symptoms and craving.

Delivering patient centered HCV-PWUD care (part two of this thesis)

In many countries, including the Netherlands, management of HCV among PWUD remains a challenge (7, 19-21). Although the advent of DAAs has made viral clearance readily achievable, elimination requires more than pharmacological efficacy. Frequent screening, lowering care thresholds and simplifying care are deemed essential for reaching the WHO goals (16). In order to reach PWUD, a patient-centered health care approach, improved access to care, and innovative care delivery models are needed (22). Care decentralization initiatives lower the threshold to care by transferring HCV treatment to non-hospital (i.e. addiction) services, with specialist HCV care in a more consultative role (23, 24). A meta-analysis by Oru and colleagues compared decentralization initiatives. Partial decentralization included testing on a decentralized site and referral elsewhere for treatment, while full decentralization included testing and treatment at the same site. Results showed linkage to care in full decentralization was 72% versus 53% in partial, and 47% in no decentralization. Treatment uptake showed comparable percentages. Similar SVR rates were achieved by decentralization of care and treatment by a non-specialist compared to treatment delivered by specialists (24).

In the Netherlands, optimization of the care pathway for PWUD has been ongoing since before DAA introduction. Most recently, the “Breakthrough Project”, executed in 2013-2016, evaluated and improved the HCV standard of care in addiction centers and distinguished 4 stages in the care pathway: 1: Case finding & pre-test counseling; 2: Testing & post-test counseling; 3: Treatment; 4: Post treatment care (25). Dedicated teams reached consensus on best practices and formulated action plans to optimize all four stages. These insights were collected in a blueprint for HCV management in Dutch addiction care (26). This blueprint coincided with the introduction of DAAs. As a result, this blueprint could not fully utilize the capabilities of DAAs in the treatment stage. So, although major strides have been made, no fully decentralized HCV care model for PWUD has been implemented in the Netherlands. This gap may result in continued fragmentation of care, leading to delays in treatment initiation, increased loss to follow-up, and missed opportunities for HCV elimination among PWUD, increasing disease burden and hindering progress toward HCV elimination targets.

Aims and outline of this thesis

The two central aims of this thesis are 1) to study interactions between addiction and HCV and 2) to explore how HCV care can be effectively operationalized within the

context of Dutch addiction care. The ultimate goal is to provide actionable insights into how addiction care can contribute to the effort toward HCV elimination.

Part one: Addiction and hepatitis C, two interacting conditions

In part one of this thesis we address two knowledge gaps regarding the complex interplay between addiction and HCV. **Chapter 2** describes national hospital healthcare utilization patterns for viral hepatitis among people with comorbid addiction diagnoses, exploring whether an addictive disorder is associated with suboptimal care. To identify whether people with addiction diagnoses receive suboptimal hepatitis-related specialist care in the Netherlands, we performed a national claims data study. **Chapter 3** explores the pharmacological implications of HCV treatment in patients undergoing opioid agonist therapy with methadone. This chapter investigates whether curing chronic HCV impacts methadone concentrations in a pharmacokinetic case series.

Part two: Implementing decentralized hepatitis C care in Dutch addiction care

Part two of this thesis evaluates the implementation of 'Hepatitis C Chain of Addiction Care (CAC)', the HCV care decentralization effort in the Netherlands. CAC was developed by a collaboration between HepNed and the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA). HepNed is the network of hepatologists and infectious disease physicians that also coordinated the nationwide hepatitis C retrieval program CELINE (27). The CAC model is an approach to decentralized HCV care specifically tailored to the Dutch addiction care setting, in line with regular HCV care guidelines (2, 12). CAC is a full decentralization initiative, so all phases of HCV care tasks are shifted to the addiction care physicians and nurses, from case finding in patients at risk, to counseling, testing, treatment and follow-up. All major addiction care organizations were invited to participate in CAC to achieve nationwide coverage. Implementation required a dynamic and tailored approach to the local situation in the individual addiction care center based on variation in care infrastructure and HCV experience. **Chapter 4** introduces CAC and describes the rationale and methodological basis of the implementation strategy in a study protocol, combining anticipated quantitative and qualitative outcomes into a representation according to the *Reach-Effectiveness-Adoption-Implementation-Maintenance* (RE-AIM) framework. RE-AIM is a widely used implementation science framework designed to assess the real-world applicability of health interventions (28-30). RE-AIM facilitates the systematic evaluation of both individual-level and organizational-level outcomes and helps to identify barriers and facilitators to successful implementation and sustainability of interventions. In **chapter 5**

we present the real-world quantitative outcomes of CAC, most importantly the elimination rate, defined as the percentage of HCV-positive patients that reached SVR. **Chapter 6** describes qualitative themes relevant to successful implementation of CAC as collected in semi-structured interviews with stakeholders.

Table 1. Summary of research questions addressed in this thesis

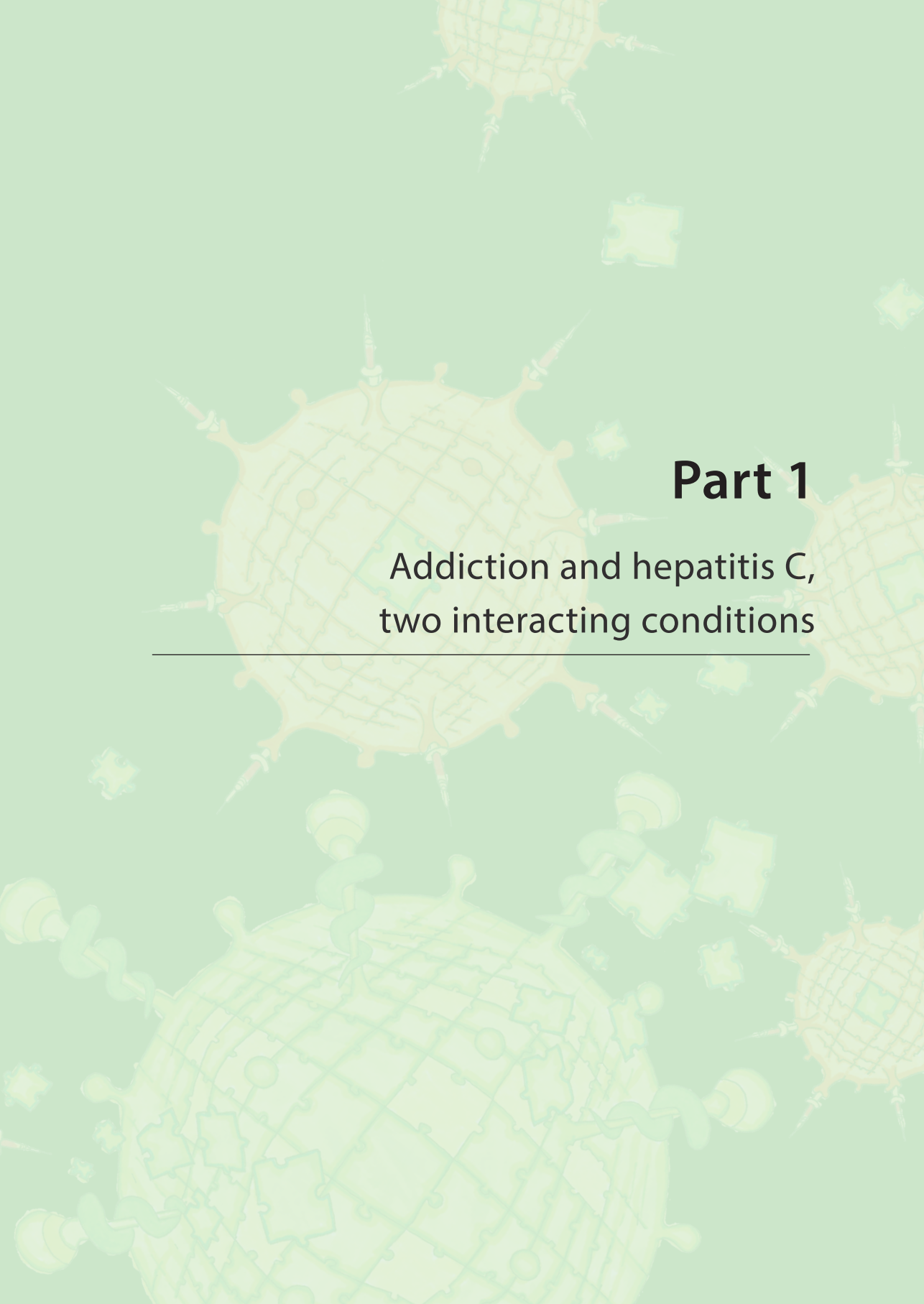
Summary of research questions and methodology of this thesis				
	#	Research question	Study design	Measures/outcomes
PART 1	2	• Is a medical history of an addictive disorder associated with suboptimal hospital hepatitis healthcare utilization?	• Retrospective cohort study using national claims data	• Odds of suboptimal care
	3	• What is the effect of HCV treatment on methadone pharmacokinetics?	• Pharmacokinetic case series	• Change in methadone plasma levels before and after treatment
	4	• To describe the methods, the project and the RE-AIM dimensions of CAC*.	• Study protocol (for chapter 5 and 6)	• n.a.
PART 2	5	• What is the reach of CAC? • How effective is the CAC model? • To what extent is CAC adopted by addiction care organizations? • Adherence to CAC model	• Multi-center prospective cohort study and • organizational level RE-AIM dimensions	• Patients tested, % positive • Elimination rate (% of HCV-positive patients that reached SVR) • Participation of centers and sites • Adherence to the protocol
	6	• What are the facilitators and barriers to implementing HCV care in addiction care?	• Qualitative interview study	• Facilitators and barriers as identified by stakeholders

*Hepatitis C Chain of Addiction Care, the HCV care decentralization effort in the Netherlands

References

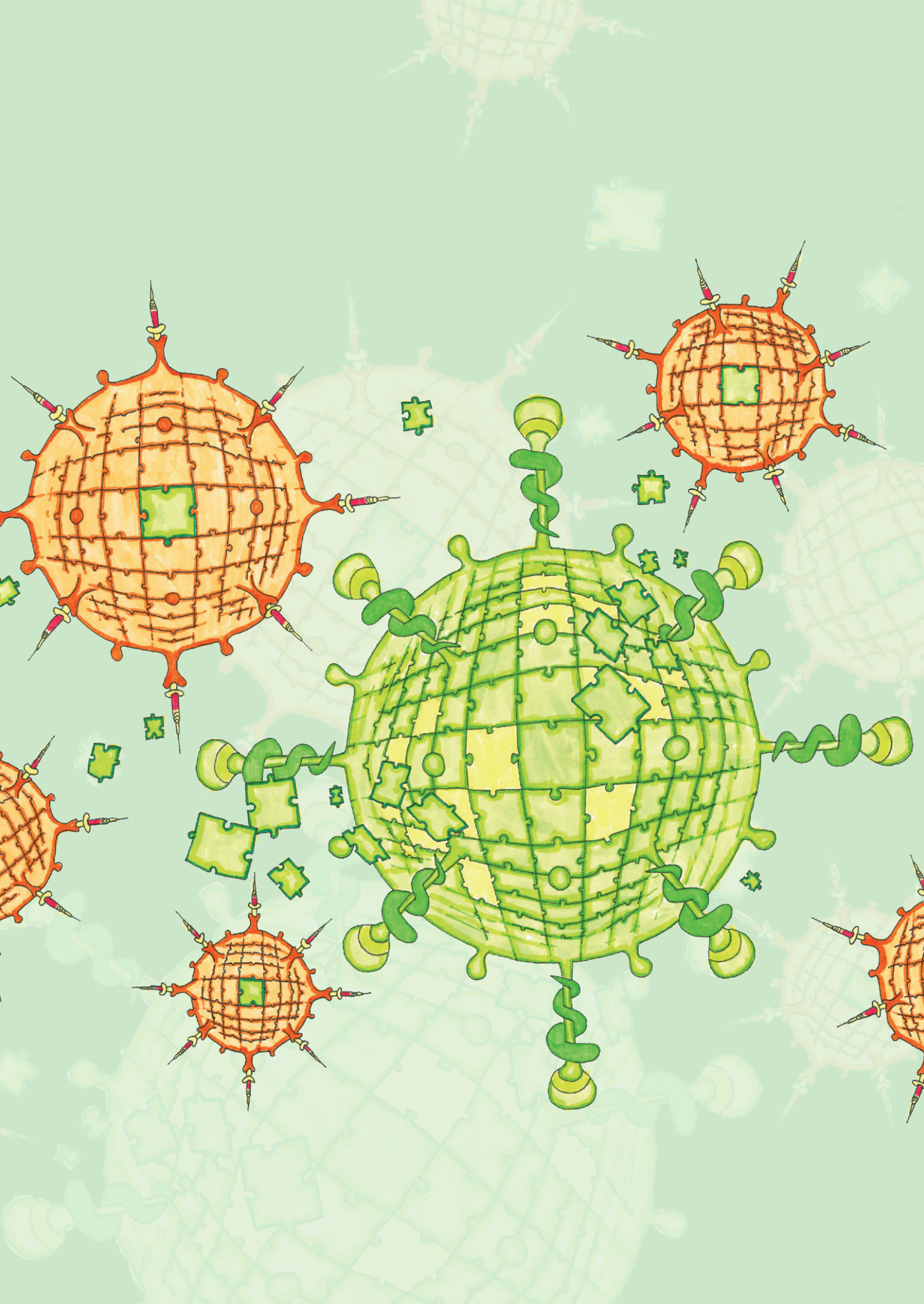
1. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. *The Lancet*. 2019; 394(10207):1451-66.
2. EASL Clinical Practice Guidelines Panel C, representative EGB, Panel m. EASL recommendations on treatment of hepatitis C: Final update of the series(). *J Hepatol*. 2020;73(5):1170-218.
3. European Association of the Study of the Liver. 2011 European Association of the Study of the Liver hepatitis C virus clinical practice guidelines. *Liver Int*. 2012;32 Suppl 1:2-8.
4. WHO. Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: WHO. 2016.
5. Razavi H. Global Epidemiology of Viral Hepatitis. *Gastroenterol Clin North Am*. 2020;49(2):179-89.
6. Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. *Epidemiol Infect*. 2019;147:e147.
7. van Dijk M, Brakenhoff SM, Isfordink CJ, Cheng WH, Blokzijl H, Boland G, et al. The Netherlands Is on Track to Meet the World Health Organization Hepatitis C Elimination Targets by 2030. *J Clin Med*. 2021;10(19).
8. Kracht PAM, Arends JE, van Erpecum KJ, Urbanus A, Willemse JA, Hoepelman AIM, et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. *Hepatol Med Policy*. 2018;3:12.
9. Van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M, Amsterdam C. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007;102(9):1454-62.
10. (LOI) Loi. LCI-richtlijn hepatitis C RIVM2019 [updated 24-09-2019. Available from: <https://lci.rivm.nl/richtlijnen/hepatitis-c>.
11. Nationale Drug Monitor. Opiaten 5.6 Hulpvraag en incidenten - Nationale Drug Monitor: Trimbos-instituut, Utrecht & WODC, Den Haag; 2022 [Available from: <https://www.nationaledrugmonitor.nl/opiaten-hulpvraag-en-incidenten/>.
12. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology*. 2020;71(2):686-721.
13. Schatz E. IDPC Briefing Paper The Dutch treatment and social support system for drug users. International Drug Policy Consortium. 2011.
14. Degenhardt L, Webb P, Colledge-Frisby S, Ireland J, Wheeler A, Ottaviano S, et al. Epidemiology of injecting drug use, prevalence of injecting-related harm, and exposure to behavioural and environmental risks among people who inject drugs: a systematic review. *Lancet Glob Health*. 2023;11(5):e659-e72.
15. Madden A, Hopwood M, Neale J, Treloar C. Beyond interferon side effects: What residual barriers exist to DAA hepatitis C treatment for people who inject drugs? *PLoS One*. 2018;13(11):e0207226.
16. van Dijk M, Drenth JPH, HepNed study g. Loss to follow-up in the hepatitis C care cascade: A substantial problem but opportunity for micro-elimination. *J Viral Hepat*. 2020;27(12):1270-83.
17. Marshall AD, Grebely J, Dore GJ, Treloar C. Barriers and facilitators to engaging in hepatitis C management and DAA therapy among general practitioners and drug and alcohol specialists-The practitioner experience. *Drug Alcohol Depend*. 2020;206:107705.

18. Smolders EJ, Pape S, de Kanter CT, van den Berg AP, Drenth JP, Burger DM. Decreased tacrolimus plasma concentrations during HCV therapy: a drug-drug interaction or is there an alternative explanation? *Int J Antimicrob Agents*. 2017;49(3):379-82.
19. Gamkrelidze I, Pawlotsky JM, Lazarus JV, Feld JJ, Zeuzem S, Bao Y, et al. Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. *Liver Int*. 2021;41(3):456-63.
20. Kim JU, Ingiliz P, Shimakawa Y, Lemoine M. Improving care of migrants is key for viral hepatitis elimination in Europe. *Bull World Health Organ*. 2021;99(4):280-6.
21. Maticic M, Cernosa J, Loboda C, Tamse J, Rigoni R, Duffell E, et al. How far are we? Assessing progress in hepatitis C response towards the WHO 2030 elimination goals by the civil society monitoring in 25 European countries, period 2020 to 2023. *Harm Reduct J*. 2024;21(1):203.
22. Von den Hoff DW, Berden FAC, Schellekens AFA. If the mountain won't come to Mohammed, then Mohammed must go to the mountain: Decentralisation of hepatitis C care for people who use drugs. *United European Gastroenterol J*. 2021.
23. Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. *BMC Health Serv Res*. 2019;19(1):765.
24. Oru E, Trickey A, Shirali R, Kanters S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health*. 2021;9(4):e431-e45.
25. Kracht PAM, de Gee EA, van der Poel A, Verhagen M, Hoepelman AIM, Croes EA, et al. Introducing hepatitis C virus healthcare pathways in addiction care in the Netherlands with a Breakthrough project: a mixed method study. *Harm Reduct J*. 2019;16(1):45.
26. Trimbos. Blueprint – Hepatitis C care pathway for clients in addiction care. Utrecht; 2017.
27. Isfordink CJ, van Dijk M, Brakenhoff SM, Kracht PAM, Arends JE, de Knegt RJ, et al. Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination. *Eur J Intern Med*. 2022.
28. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. *Front Public Health*. 2019;7:64.
29. Holtrop JS, Estabrooks PA, Gaglio B, Harden SM, Kessler RS, King DK, et al. Understanding and applying the RE-AIM framework: Clarifications and resources. *J Clin Transl Sci*. 2021;5(1):e126.
30. Sweet SN, Ginis KA, Estabrooks PA, Latimer-Cheung AE. Operationalizing the RE-AIM framework to evaluate the impact of multi-sector partnerships. *Implement Sci*. 2014;9:74.



Part 1

Addiction and hepatitis C, two interacting conditions



Chapter 2

Against All Odds? Addiction History Associated with Better Viral Hepatitis Care: A Dutch Nationwide Claims Data Study

Daan W. Von den Hoff

Floor A. C. Berden

Femke Atsma

Arnt F. A. Schellekens

Joost P. H. Drenth

Abstract

The elimination of viral hepatitis in target populations is crucial in reaching WHO viral hepatitis elimination goals. Several barriers for the treatment of viral hepatitis in people with addictive disorders have been identified, yet nationwide data on hepatitis healthcare utilization (HCU) in these patients are limited. We investigated whether a history of addictive disorder is associated with suboptimal hepatitis HCU, indicating failure to receive diagnostic care or treatment. We identified all newly referred viral hepatitis patients in the Netherlands between 2014 and 2019 by query of the Dutch national hospital claims database. Each patient's first year of HBV or HCV care activities was collected and clustered in two categories, 'optimal' or 'suboptimal' hepatitis HCU. Optimal HCU includes antiviral therapy. We tested the association between addiction history and HCU, adjusted for sex, age, migrant status, and comorbidity. In secondary analyses, we explored additional factors affecting hepatitis HCU. We included 10,513 incident HBV and HCV patients, with 13% having an addiction history. Only 47% of all patients achieved optimal hepatitis HCU. Addiction history was associated with less suboptimal HCU (adjusted OR = 0.73, 95% CI = 0.64–0.82). Migration background was associated with suboptimal HCU (OR = 1.62, 95% CI = 1.50–1.76). This study shows that addiction history is associated with higher viral hepatitis HCU; thus, this population performs better compared to non-addicted patients. However, less than 50% of all patients received optimal hepatitis care. This study highlights the need to improve hepatitis HCU in all patients, with a focus on migrant populations. Linkage to care in the addicted patients is not studied here and may be a remaining obstacle to be studied and improved to reach WHO viral hepatitis elimination goals.

Introduction

Patients with a chronic hepatitis infection are at risk of developing severe long-term liver-related complications including liver cirrhosis and hepatocellular carcinoma. In recent years, both hepatitis B (HBV) and C (HCV) virus infections have become manageable with drugs that suppress the hepatitis B virus and even cure patients in the case of HCV (1, 2). The worldwide prevalence of chronic HBV and HCV is around 3.9% and 1.0%, respectively (3). In most Western countries, the prevalence of viral hepatitis is lower, and in the Netherlands, it is estimated to be around 0.3% (4). In 2016, the World Health Organization (WHO) set ambitious goals for the elimination of HBV and HCV by 2030 (5). Key to the target in this elimination strategy are specific populations, where the prevalence rates are higher, in particular migrants from endemic countries and people who inject(ed) drugs (PWID) (4, 6). For instance, in the Netherlands prevalence rates for HBV and HCV among PWID are up to 4% and 59%, respectively (4). Treating this population, as part of a micro-elimination strategy, is crucial to reach WHO goals (7).

HBV and HCV elimination in PWID is challenging, as studies among PWID show mediocre rates of treatment initiation, varying between 20%–90% (8-15). Failure to initiate treatment puts patients at a risk of liver-related complications and maintains a viral reservoir. Several reasons have been put forward to explain low treatment rates in PWID, such as absence of insurance coverage (16), logistic inability to utilize care services outside the patient's community (17), and personal barriers for engaging in testing and treatment (18-20). Treating physicians might also experience barriers for treatment initiation in PWID, as they may deem them incapable of adhering to treatment (19, 21, 22). The ultimate fallout might be that PWID with chronic HBV or HCV underutilize hospital care and thus remain infected. To our knowledge, no data on PWID HBV and HCV healthcare utilization (HCU) are yet available.

Dutch HBV and HCV care is primarily provided in hospitals, so utilization of hospital diagnostic and treatment services is essential for the elimination of HBV and HCV. The aim of this study was to compare the HBV and HCV-related healthcare utilization (HCU) in patients with an addiction history (AH+) versus the non-addicted population (AH-) using a national healthcare claims database in the Netherlands. We opted for AH as the variable of interest, while potential addiction-associated barriers to participate in hospital care determine HCU in PWID, not injecting drug use per se. Moreover, in the Dutch viral hepatitis population, injecting drug use is the most likely cause of infection when addiction is present (23). We hypothesized that a history of addiction is associated with suboptimal HCU.

Methods

Data Source

We used hospital claims data in the Netherlands from the years 2012–2019 as provided by Statistics Netherlands (CBS) (24). This database consisted of anonymized diagnoses and treatment codes ('DBC') and all underlying diagnosis and treatment-related healthcare activities in hospital and addiction care. The database has a 99% coverage of the Dutch population, varying by year of submission 92.8–99.9% (25, 26).

Diagnoses dated from 1 January 2012 up to 31 December 2019 were available in this database. In addition, age, sex, country of birth, and medication prescriptions were also available. In the Netherlands, addiction care is widely available and generally provided in low threshold, dedicated addiction care facilities, focusing on prevention and harm reduction (27, 28). They are a part of insured mental healthcare. Claims and diagnosis labels from these facilities were available in the database as well. Addiction history (AH+/-) was collected from these mental healthcare claims data.

Study Population

We selected all insured patients with available HBV or HCV diagnoses in Dutch hospitals from 2012 up to and including 2019. Hepatitis treatment was not performed by general practitioners or other primary care physicians in the timeframe this database covers. To identify a new referral, we excluded patients with an HBV/HCV diagnosis prior to 1 January 2014. Patients with an incident diagnosis after 01-01-2019 were excluded to ensure one year of follow-up, and patients could not be included twice (reinfection). The date of the first claim with an HBV or HCV diagnosis label was defined as the index date. Demographic data for all included patients were collected. Migrant status was defined as not born in the Netherlands. This database contains only documented migrant populations, these patients have full Dutch health care coverage (25). Comorbid diagnoses, based on hospital care diagnosis labels, were organized according to the Charlson comorbidity index (29). No distinction between HBV and HCV could be made based on diagnosis label, so we used HBV/HCV specific medication and ICD10 codes if available in order to characterize the type of infection. All individuals with at least one DBC claim from an addiction care center were allocated to the 'AH+' subgroup. Patients under 18 years old at the time of referral were excluded.

Outcomes and Clustering Healthcare Activities

The primary outcome is the odds of suboptimal viral hepatitis-related HCU in the first year after the index date for patients with and without AH. To describe and

compare hepatitis HCU, all registered healthcare activities within HBV or HCV claims were aggregated to representative categories. Based on HBV and HCV guidelines [1,2,25,26], we constructed HCU stages with incremental adherence to the most optimal diagnostic and treatment trajectory. This was performed in collaboration with a panel of Dutch hepatitis experts. We presented the stages to the panel, which resulted in a hybrid review process. Agreement was reached in the form of our initial proposal, and it was not adjusted during review. The final outcome determined the conclusive definition for the endpoint. We distinguished optimal hepatitis HCU and suboptimal HCU. Suboptimal care was further divided into grade I (mild) and grade II (severe) suboptimal care for our subgroup analysis.

Patients in the 'optimal care' HCU category were defined as having visited the outpatient clinic more than twice and/or received laboratory tests more than twice and/or underwent abdominal radiology (i.e. sonography) or biopsy (to assess liver fibrosis or cirrhosis) and had been prescribed HBV or HCV medication. Patients with 'grade I suboptimal care' were defined as having received the same diagnostic care as the optimal group but did not initiate treatment. 'Grade II suboptimal care' was defined as loss to follow-up early in the diagnostic chain (maximum of two outpatient visits and two laboratory tests and no other care).

We anticipated that physicians may have stalled treatment initiation in the years prior to direct-acting antiviral (DAA) availability and reimbursement in late 2015. To adjust for this potential confounding effect, we included all medication prescriptions up to 31 December 2016 in patients diagnosed before 1 January 2016. A detailed description of all categories of HCU can be found in Supplement Table S1.

Statistical Analyses

Baseline characteristics were summarized as percentages, means (with SD), or medians (IQR), depending on the variable and its distribution. Abdominal radiology, other interventions, and pathologic assessment were summarized as percentage of patients that underwent at least one activity in the subgroup. Odds for suboptimal HCU were compared between patients with and without a history of addiction treatment, using binary logistic regression analyses, while taking age, sex, migrant status, and comorbid conditions (especially HIV) into account. First, we tested the association between addiction history and suboptimal HCU. Second, we tested the association between addiction history and grade II suboptimal HCU in the subgroup of patients who received suboptimal care. A sensitivity analysis was performed by substituting addiction history (AH+) with a history of opioid use disorder as determinant. Since no data on injecting drugs were available in the CBS

national claims database, and the most commonly injected drug in the Netherlands is opioids, a history of opioid use disorder might best describe the PWID population within viral hepatitis patients. This sensitivity analysis adds external validity to our results, as in literature the determinant is often PWID (1, 2, 4, 20, 30-32).

We explored additional factors influencing HCU in a secondary analysis, using backward stepwise regression analysis. Outcomes are presented as odds ratios. All analyses were performed using Statistical Package for the Social Sciences version 25.

Results

Study Population

We identified 19,992 patients with an HBV or HCV diagnosis from 2012 to 2019 in our database. The number of new diagnoses remained relatively stable at around 2100 (range 1933–2430) per year (Supplement Table S2). After exclusion, 10,513 newly referred patients were included (Figure 1). The majority of patients was male (62%) and mean age was 47.5 years old (SD: 13.6). Some 13% ($n = 1371$) of the included patients had a history in addiction care (AH+). Demographic data and comorbid conditions are shown in Table 1. The majority of viral hepatitis patients had a migration background (63.1%), with more migrants in the AH– hepatitis population than in the AH+ patients (68.0% vs. 32.2%). Patients with a migration background mainly originated from Africa or Asia (64.2%) and Eastern Europe (15.3%). Malignant disease was the most prevalent registered comorbid condition in our viral hepatitis population (6.4%), followed by HIV/AIDS (5.3%). Liver cirrhosis was more prevalent in AH+ patients than in AH– patients (4.7% vs. 2.4%). Although a distinction could not be made in 30% of patients, our data suggest that HCV and HBV distribution were different in AH+ patients compared to AH– patients, with more HCV in AH+ (72% vs. 34%) and more HBV in AH– (32% vs. 4%) (Table 1).

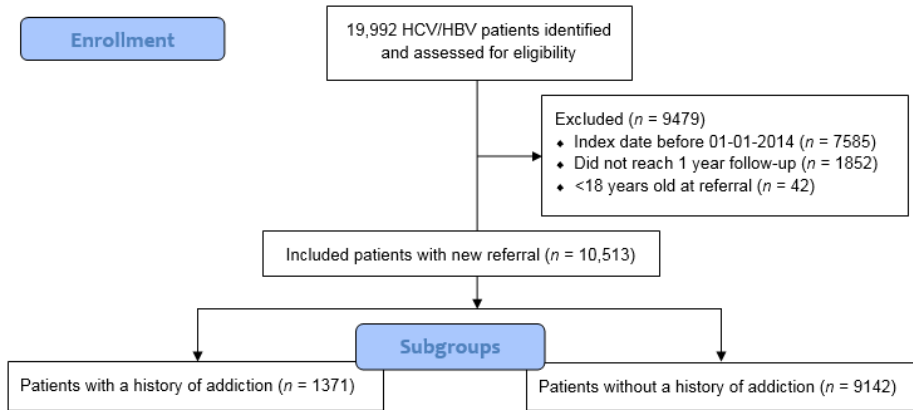


Figure 1. Patient flowchart.

Table 1. Baseline characteristics.

	Total n (%)	AH+ n (%)	AH- n (%)
Total	10,513	1371 (13.0)	9142 (87.0)
Male	6521 (62.0)	1090 (79.5)	5431 (59.4)
Age at diagnosis (y) (SD)	47.49 (13.6)	50.48 (9.0)	47.04 (14.1)
Comorbid conditions (any):	2190 (20.8)	360 (26.3)	1830 (20.0)
Liver cirrhosis	282 (2.7)	65 (4.7)	217 (2.4)
Malignancy	677 (6.4)	86 (6.3)	591 (6.5)
HIV/AIDS	552 (5.3)	85 (6.2)	467 (5.1)
Chronic obstructive pulmonary disease (COPD)	217 (2.1)	95 (6.9)	122 (1.3)
Diabetes	198 (1.9)	17 (1.2)	181 (2.0)
Migrant status:*	6636 (63.1)	441 (32.2)	6195 (68.0)
Western Europe	235 (3.5)	59 (13.4)	176 (2.8)
Northern Europe	132 (2.0)	26 (5.9)	106 (1.7)
Southern Europe	273 (4.1)	52 (11.8)	221 (3.6)
Eastern Europe	1014 (15.3)	88 (20.0)	926 (14.9)
Africa	1656 (25.0)	62 (14.1)	1594 (25.7)
Asia	2603 (39.2)	65 (14.7)	2538 (41.0)
Other **	723 (10.9)	89 (20.2)	634 (10.2)
Type of viral hepatitis			
HCV	4105 (39.0)	992 (72.4)	3113 (34.1)
HBV	2978 (28.3)	56 (4.1)	2922 (32.0)
HCV + HBV co-infection	285 (2.7)	28 (2.0)	257 (2.8)
Unknown	3145 (29.9)	295 (21.5)	2850 (31.2)

*28 patients' country of birth was missing; ** North America, South America, and Oceania; SD = standard deviation; AH = addiction history.

Healthcare Utilization (HCU)

All aggregated healthcare activity categories showed a skewed distribution (Table 2). AH+ patients had a median of four outpatient visits compared to three in AH– patients. Both subgroups underwent a median of two venipunctures. Abdominal radiology (67.5% vs. 63.4%) and other interventions, i.e. endoscopic or surgical procedures (13.6% vs. 8.9%), were more frequently seen in AH+ patients.

Table 2. Healthcare activities per category.

Category	TotalMedian (IQR)	AH+Median (IQR)	AH–Median (IQR)
Outpatient visits	3 (2–6)	4 (2–6)	3 (2–6)
Venipunctures	2 (1–4)	2 (1–4)	2 (1–4)
Lab tests	19 (4–42)	24 (6–46)	19 (4–41)
Radiology(abdominal) *	63.9%	67.5%	63.4%
Other interventions (i.e., endoscopy) *	9.5%	13.6%	8.9%
Pathology *	3.2%	3.0%	3.2%

* % of patients that underwent at least 1 activity;IQR = interquartile range.

Table 3. A: Association between history of an addictive disorder and suboptimal (I + II) healthcare utilization. B: Association between history of an addictive disorder and grade II suboptimal healthcare utilization as opposed to grade I suboptimal HCU.

(A)						
Factor	OR ^a (univariate)	95% CI ^a	p	aOR ^{ab} (multivariate)	95% CI	p
Addiction history	0.60	(0.54, 0.67)	<0.0001	0.73	(0.64–0.82)	<0.0001
(B)						
Factor	OR ^a (univariate)	95% CI ^a	p	aOR ^{ab} (multivariate)	95% CI	p
Addiction history	1.35	(1.12, 1.63)	0.0020	1.15	(0.94–1.40)	0.17

^a OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio. ^b Adjusted for sex, age, migrant status, cirrhosis, diabetes, COPD, malignancy, HIV. Optimal = diagnosed and treated; suboptimal I = diagnosed and followed-up; suboptimal II = only diagnosed.

We found that AH+ patients more often received optimal care than AH– patients (57.9% vs. 45.2%) (Figure 2 and Supplement Table S3). Binary logistic regression analysis demonstrated lower odds for suboptimal HCU in AH+ patients compared with AH– patients after adjusting for other variables (aOR = 0.73, 95% CI = 0.64–0.82) (Table 3). In the subgroup of patients with suboptimal HCU, addiction history had an unadjusted association with grade II suboptimal care (OR = 1.35, 95%

CI = 1.12–1.63); however, this effect disappeared after adjustment for potential confounding variables (aOR = 1.13, 95% CI = 0.93, 1.38; Table 3). The sensitivity analysis with history of opioid use disorder instead of addictive disorder in general did not alter the results (Supplement Table S4).

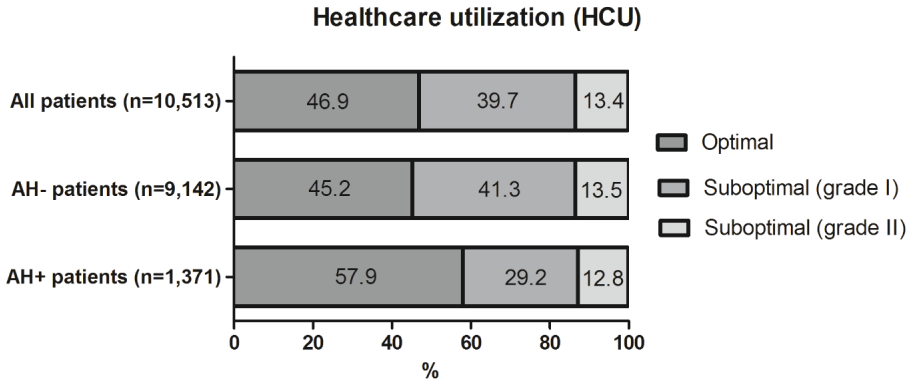


Figure 2. Viral hepatitis-related healthcare utilization.

Exploratory Model

Our exploratory logistic regression model, testing other factors for an association with suboptimal hepatitis HCU, showed that migration background increased the odds for suboptimal HCU (OR = 1.19, 95% CI = 1.09–1.30). Multivariate analysis also identified COPD to be associated with suboptimal HCU (aOR = 1.44, 95% CI = 1.09–1.91) (Figure 3). All other factors decreased the odds of suboptimal HCU (Figure 3 and Supplement Table S5.1).

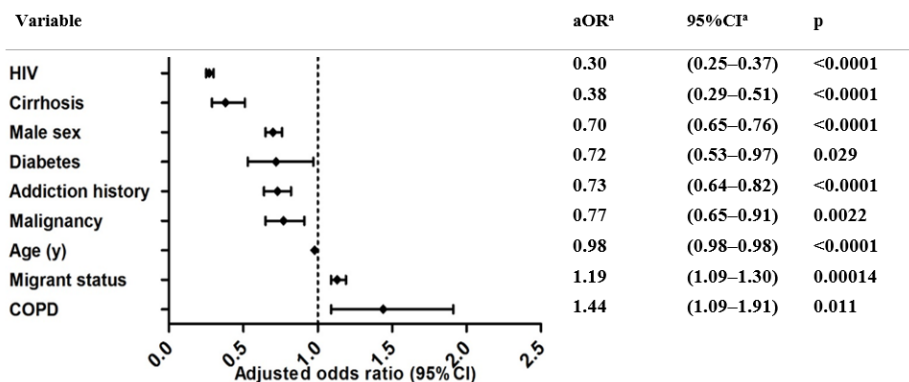


Figure 3. Identification of factors contributing to suboptimal (I + II) hepatitis HCU. a: OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio; adjusted for sex, age, migrant status, cirrhosis, diabetes, COPD, malignancy, HIV. Optimal = diagnosed and treated; suboptimal I = diagnosed and followed-up; suboptimal II = only diagnosed.

When exploring patient characteristics associated with grade II suboptimal hepatitis HCU as opposed to grade I suboptimal HCU, migration background decreased the odds for grade II suboptimal HCU (OR = 0.64, 95% CI = 0.57–0.73), while age and HIV status increased the odds of grade II suboptimal HCU (Supplement Table S5.2) (Figure 4).

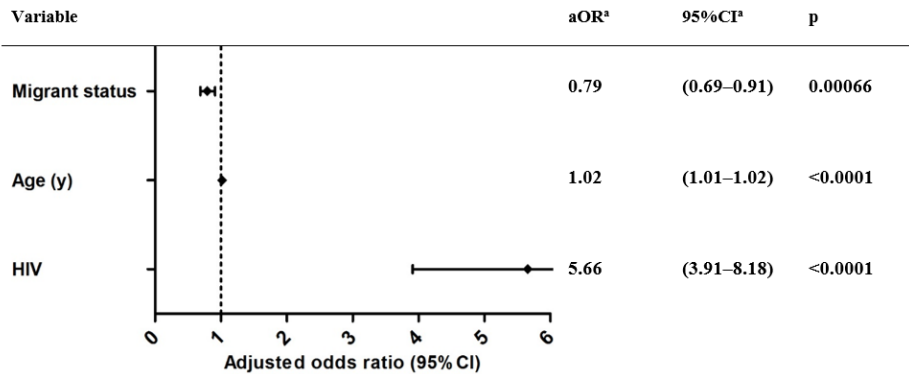


Figure 4. Identification of factors contributing to grade II suboptimal hepatitis HCU. a: OR = odds ratio; CI = confidence interval; aOR = adjusted odds ratio; adjusted for sex, age, migrant status, cirrhosis, diabetes, COPD, malignancy, HIV. Optimal = diagnosed and treated; suboptimal I = diagnosed and followed-up; suboptimal II = only diagnosed.

Discussion

This study shows that HCU in the Dutch patients with an addiction history is better compared to those without a history of addiction. Our exploratory analysis suggests that, among referred viral hepatitis patients, a migration background is associated with suboptimal hepatitis HCU. Overall, optimal viral hepatitis HCU in the first year after referral was low at 47%, so increased efforts to achieve optimal care in all viral hepatitis patients is warranted.

Our findings indicate that enrolment in Dutch addiction care for addiction to any substance predicts better HCU for viral hepatitis compared to those without a history of addiction. The association between addiction and optimal HCU contrasts with our hypothesis and existing literature linking PWID with poor HBV and HCV care outcomes. In the literature, PWID are found to perform worse in treatment initiation for viral hepatitis (8, 10, 12, 22). There are a few possible explanations for this discrepancy. Most importantly, in the Netherlands, addiction care is provided through specialized addiction care facilities, and it is insured and widely available (27, 28). These facilities provide needle exchange programs, access to opioid substitution therapy with methadone, buprenorphine, and heroin-assisted

treatment (23, 33). These interventions facilitate low threshold monitoring and education of the addicted population on topics such as viral hepatitis, potentially contributing to more optimal hepatitis HCU. Addiction might influence HCU more in countries without the aforementioned interventions, and policymakers should therefore consider implementing such programs. Second, this study did not include patients who were never referred for hepatitis care and for whom a hospital claim is therefore absent. Although not studied here, a previous study has identified this linkage-to-care problem in Dutch addiction care centers (7). What we can conclude, however, is that there is no reason to withhold viral hepatitis patients with comorbid addiction from referral for hepatitis care and that stigmatization toward the addicted population in terms of hepatitis HCU is unjustified and should be avoided at all times. Reduced stigmatization and efforts to increase linkage to care will result in higher treatment initiation and completion rates for the addicted population, further approaching the WHO goals of viral elimination.

Nearly two-thirds of the viral hepatitis population in our database had a migration background. The association between migration background and suboptimal HCU found in our exploratory analysis is the major contributor to the observed low overall rate of optimal HCU (47%). Other contributors may be HBV patients without an indication for treatment or HCV patients who cleared the infection spontaneously; both are presumably present in a limited number of patients. The migrant population might fail to achieve optimal HCU due to a mix of barriers for hepatitis HCU, such as language and insurance issues (34, 35). Interestingly, we found that within the suboptimal HCU group, migrant status increased the odds of grade I suboptimal HCU and not grade II suboptimal HCU, indexed by early drop-out during the diagnostic trajectory. This suggests that patients with a migration background receive adequate diagnostic care but fail to initiate treatment. This finding calls for a need to better facilitate viral hepatitis treatment for this population. The opposite HCU effect was found in HIV-positive patients, as HIV status was strongly associated with optimal hepatitis HCU (OR: 3.33). However, when only patients with suboptimal HCU were analyzed, HIV was associated with grade II suboptimal HCU and thus loss to follow-up (OR: 5.9). This could be explained by the structured combined HIV and viral hepatitis care in Dutch HIV care facilities, contributing to more optimal hepatitis HCU. At the same time, if HIV-positive patients withdraw from healthcare, they seem to completely stop visiting the hospital, dropping out of viral hepatitis care. Besides migration background, COPD was also associated with suboptimal HCU. Only 2% of patients had a COPD medical history in the hospital, and many patients may be under COPD care in the non-hospital setting, so the relevance and generalizability of this finding are unknown.

This study's key strength is its national coverage, resulting in a large sample size and representative sample. Since the Netherlands has a relatively low number (0.145%) of uninsured persons, our study population in fact reflects the actual population (36). The source data themselves are reliable, as they contain a centralized extensive overview of Dutch hospital care, as well as detailed information on addiction care claims. Furthermore, for our primary outcome, we performed logistic regression to take potential confounding effects of other factors into account. Lastly, we performed an explorative analysis to complement our findings and to provide guidance for future research and public health policymakers.

This study also comes with limitations. Our outcomes are based on a variety of healthcare activity data, which we aggregated and constructed into representative stages of HCU (optimal, grade I suboptimal, grade II suboptimal). Though these categories were established in close collaboration with a panel of hepatitis treatment experts, increasing validity, it may not apply to other countries with different data registries. This method may be hard to replicate in other countries with different data registries. Secondly, there was no option to isolate PWID in our database and specifically test for an association between injecting drugs and hepatitis HCU. Though our sensitivity analysis, only testing an association among viral hepatitis patients with a history of opioid use disorder, did not alter the results, future studies may specifically look at PWID instead of addiction history. Another important limitation is the absence of a distinction between HCV and HBV infection in our database. This could be relevant, as HBV patients without an indication for treatment or HCV patients who cleared the infection spontaneously will have lowered our 'optimal care' outcome. Lastly, linkage to care is an important topic in viral hepatitis care for the addicted population and was not studied here, as primary care data were unavailable. As mentioned before, we believe the linkage-to-care issue may be substantial in the Dutch addicted population (7). The most recent estimate of the Dutch HBV and HCV PWID population size in 2016 is 3640 (low–high estimate 2152–6056), while we retrieved 1371 patients with an addiction history from our national hospital database (4).

To summarize, in contrast to our hypothesis, a history of an addictive disorder is associated with less suboptimal hepatitis HCU in patients initiating hepatitis B and C care in the Netherlands. However, it must be noted that, overall, less than half of all patients initiating care for viral hepatitis received optimal hepatitis care. A migrant background was the most relevant factor contributing to suboptimal HCU. To reach WHO goals of viral elimination in the Netherlands, we recommend endeavors to increase hepatitis HCU, most importantly treatment initiation in all viral hepatitis

patients, with extra focus on populations with a migration background. Efforts to eliminate HBV and HCV among PWID should focus on linkage to care, as we found that once patients with a history of addictive disorders are linked to care, they perform relatively well in terms of HCU. Stigma towards this population in terms of healthcare utilization is therefore unjustified. In countries without the availability of low threshold, insured addiction care, development of these services might provide an important vehicle for reaching WHO viral elimination for PWID.

References

1. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol.* 2018;69(2):461-511.
2. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(2):370-98.
3. Razavi H. Global Epidemiology of Viral Hepatitis. *Gastroenterol Clin North Am.* 2020;49(2):179-89.
4. Koopsen J, van Steenberghe JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. *Epidemiol Infect.* 2019;147:e147.
5. WHO. Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: WHO. 2016.
6. van Dijk M, Brakenhoff SM, Isfordink CJ, Cheng WH, Blokzijl H, Boland G, et al. The Netherlands Is on Track to Meet the World Health Organization Hepatitis C Elimination Targets by 2030. *J Clin Med.* 2021;10(19).
7. Kracht PAM, Arends JE, van Erpecum KJ, Urbanus A, Willemse JA, Hoepelman AIM, et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. *Hepatol Med Policy.* 2018;3:12.
8. Nitulescu R, Young J, Saeed S, Cooper C, Cox J, Martel-Laferrriere V, et al. Variation in hepatitis C virus treatment uptake between Canadian centres in the era of direct-acting antivirals. *Int J Drug Policy.* 2019;65:41-9.
9. Solund C, Hallager S, Pedersen MS, Fahnoe U, Ernst A, Krarup HB, et al. Direct acting antiviral treatment of chronic hepatitis C in Denmark: factors associated with and barriers to treatment initiation. *Scand J Gastroenterol.* 2018;53(7):849-56.
10. van Dijk M, Drenth JPH, HepNed study g. Loss to follow-up in the hepatitis C care cascade: A substantial problem but opportunity for micro-elimination. *J Viral Hepat.* 2020;27(12):1270-83.
11. Hajarizadeh B, Cunningham EB, Reid H, Law M, Dore GJ, Grebely J. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology.* 2018;3(11):754-67.
12. Shiha G, Soliman R, Serwah A, Mikhail NNH, Asselah T, Easterbrook P. A same day 'test and treat' model for chronic HCV and HBV infection: Results from two community-based pilot studies in Egypt. *J Viral Hepat.* 2020;27(6):593-601.
13. Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. *Clin Microbiol Rev.* 2020;33(2).
14. Allain JP, Opare-Sem O. Screening and diagnosis of HBV in low-income and middle-income countries. *Nat Rev Gastroenterol Hepatol.* 2016;13(11):643-53.
15. Locarnini S, Hatzakis A, Chen DS, Lok A. Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. *J Hepatol.* 2015;62(1 Suppl):S76-86.
16. Falade-Nwulia O, Ward KM, McCormick S, Mehta SH, Pitts SR, Katz S, et al. Network-based recruitment of people who inject drugs for hepatitis C testing and linkage to care. *J Viral Hepat.* 2020;27(7):663-70.

17. Benitez TM, Fernando SM, Amini C, Saab S. Geographically Focused Collocated Hepatitis C Screening and Treatment in Los Angeles's Skid Row. *Digestive Diseases and Sciences*. 2020;65(10):3023-31.
18. Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. *Curr Opin HIV AIDS*. 2011;6(6):501-7.
19. Grebely J, Oser M, Taylor LE, Dore GJ. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. *J Infect Dis*. 2013;207 Suppl 1:S19-25.
20. Bajis S, Grebely J, Hajarizadeh B, Applegate T, Marshall AD, Ellen Harrod M, et al. Hepatitis C virus testing, liver disease assessment and treatment uptake among people who inject drugs pre- and post-universal access to direct-acting antiviral treatment in Australia: The LiveRLife study. *Journal of Viral Hepatitis*. 2019;27(3):281-93.
21. Treloar C, Newland J, Rance J, Hopwood M. Uptake and delivery of hepatitis C treatment in opiate substitution treatment: perceptions of clients and health professionals. *J Viral Hepat*. 2010;17(12):839-44.
22. Cuomo G, Borghi V, Andreone P, Massari M, Villa E, Pietrangelo A, et al. Missed treatment in an Italian HBV infected patients cohort: HBV RER. *Dig Liver Dis*. 2016;48(11):1346-50.
23. Schreuder I, van der Sande MA, de Wit M, Bongaerts M, Boucher CA, Croes EA, et al. Seroprevalence of HIV, hepatitis b, and hepatitis c among opioid drug users on methadone treatment in the netherlands. *Harm Reduct J*. 2010;7:25.
24. Statistics Netherlands (CBS) [Available from: <https://www.cbs.nl/en-gb/onz-diensten/customised-services-microdata/microdata-conducting-your-own-research>.
25. Mszsubtrajectentab: Gesloten DBC subtrajecten [Available from: <https://www.cbs.nl/nl-nl/onz-diensten/maatwerk-en-microdata/microdata-zelf-onderzoek-doen/microdatabestanden/mszsubtrajectentab-gesloten-dbc-subtrajecten>.
26. Mszprestatiesvekttab: Geopende Diagnose Behandeling [Available from: <https://www.cbs.nl/nl-nl/onz-diensten/maatwerk-en-microdata/microdata-zelf-onderzoek-doen/microdatabestanden/mszprestatiesvekttab-geopende-diagnose-behandeling>.
27. The Netherlands Health system review The European Observatory on Health Systems2010 [Available from: https://edit-ggz-acc.azurewebsites.net/getmedia/a2213618-e5c0-42ea-9a39-20e7e9a56f2d/nivel_health-systems-in-transition_2010.pdf.
28. result of negotiations between the Dutch government, De Nederlandse ggz and eight other stakeholders; ADMINISTRATIVE AGREEMENT ON THE FUTURE OF MENTAL HEALTH CARE 2013-2014 2013 [Available from: https://edit-ggz-acc.azurewebsites.net/getmedia/b8ce998f-67af-4d43-a376-694a0e469379/ggzn_National-Agreement-on-the-Future-of-Mental-Health-Care_18062012.pdf.
29. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in Registry-based Research. *Methods Inf Med*. 2017;56(5):401-6.
30. Grebely J, Hajarizadeh B, Lazarus JV, Bruneau J, Treloar C, International Network on Hepatitis in Substance U. Elimination of hepatitis C virus infection among people who use drugs: Ensuring equitable access to prevention, treatment, and care for all. *Int J Drug Policy*. 2019;72:1-10.
31. Grebely J, Tran L, Degenhardt L, Dowell-Day A, Santo T, Larney S, et al. Association between opioid agonist therapy and testing, treatment uptake, and treatment outcomes for hepatitis C infection among people who inject drugs: A systematic review and meta-analysis. *Clin Infect Dis*. 2020.

32. Graf C, Mucke MM, Dultz G, Peiffer KH, Kubesch A, Ingiliz P, et al. Efficacy of Direct-acting Antivirals for Chronic Hepatitis C Virus Infection in People Who Inject Drugs or Receive Opioid Substitution Therapy: A Systematic Review and Meta-analysis. *Clin Infect Dis*. 2020;70(11):2355-65.
33. Van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M, Amsterdam C. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007;102(9):1454-62.
34. Seedat F, Hargreaves S, Nellums LB, Ouyang J, Brown M, Friedland JS. How effective are approaches to migrant screening for infectious diseases in Europe? A systematic review. *The Lancet Infectious Diseases*. 2018;18(9):e259-e71.
35. Kim JU, Ingiliz P, Shimakawa Y, Lemoine M. Improving care of migrants is key for viral hepatitis elimination in Europe. *Bull World Health Organ*. 2021;99(4):280-6.
36. Health insurance numbers [Available from: <https://www.zorgwijzer.nl/faq/cijfers-zorgverzekering>.

Supplementary files

Table 1. Required number of healthcare activities for healthcare utilization (HCU) outcomes.

Stage of HCU	Severe suboptimal	Mild suboptimal	Optimal
Outpatient visits	≤2 AND	>2 OR	>2 OR
Blood withdrawal	≤2 AND	>2 OR	>2 OR
interventions <i>ie. Abdominal radiology/biopsy</i>	NO AND	≥1 AND	≥1 AND
HBV/HCV Medication	NO	NO	YES

Table 2. Year of diagnosis

Year of diagnosis	All patients (%)	AH+(%)	AH-(%)
2014	2142(20.4)	275(20.1)	1867(20.4)
2015	1840(17.5)	302(22.0)	1538(16.8)
2016	2430(23.1)	359(26.2)	2071(22.7)
2017	2168(20.6)	241(17.6)	1927(21.1)
2018	1933(18.4)	194(14.2)	1739(19.0)

Table 3. HCV/HBV Healthcare utilization (HCU)

HCU	Suboptimal care		Optimal care
	Severe	Mild	
Addicted patients N (%)	176(12.8)	401(29.2)	794 (57.9)
Non-addicted patients N (%)	1231(13.5)	3775(41.3)	4136(45.2)
Total patients N(%)	1407(13.4)	4176(39.7)	4930(46.9)

Table 4.1. Sensitivity analysis. Association between opioid addiction and suboptimal healthcare utilization

Factor	OR ^a (univariate)	95%CI ^a	P value	aOR ^{ab} (multivariate)	95%CI	P value
Opioid Addiction	0.61	(0.52, 0.72)	<0.0001	0.75	(0.63, 0.89)	0.001

^a OR = Odds ratio; CI = confidence interval; aOR = adjusted odds ratio

^bAdjusted for sex, age, migrant status, comorbidities (see table2)

Table 4.2. Sensitivity analysis. Association between opioid addiction and severe suboptimal healthcare utilization within suboptimal HCU subgroup

Factor	OR ^a (univariate)	95%CI ^a	P value	aOR ^{ab} (multivariate)	95%CI	P value
Opioid Addiction	0.85	(0.63, 1.14)	0.27	0.70	(0.51, 0.95)	0.020

^a OR = Odds ratio; CI = confidence interval; aOR = adjusted odds ratio

^bAdjusted for sex, age, migrant status, comorbidities (see table2)

Table 5.1. Identification of variables contributing to HCU. Association between variables and suboptimal healthcare utilization

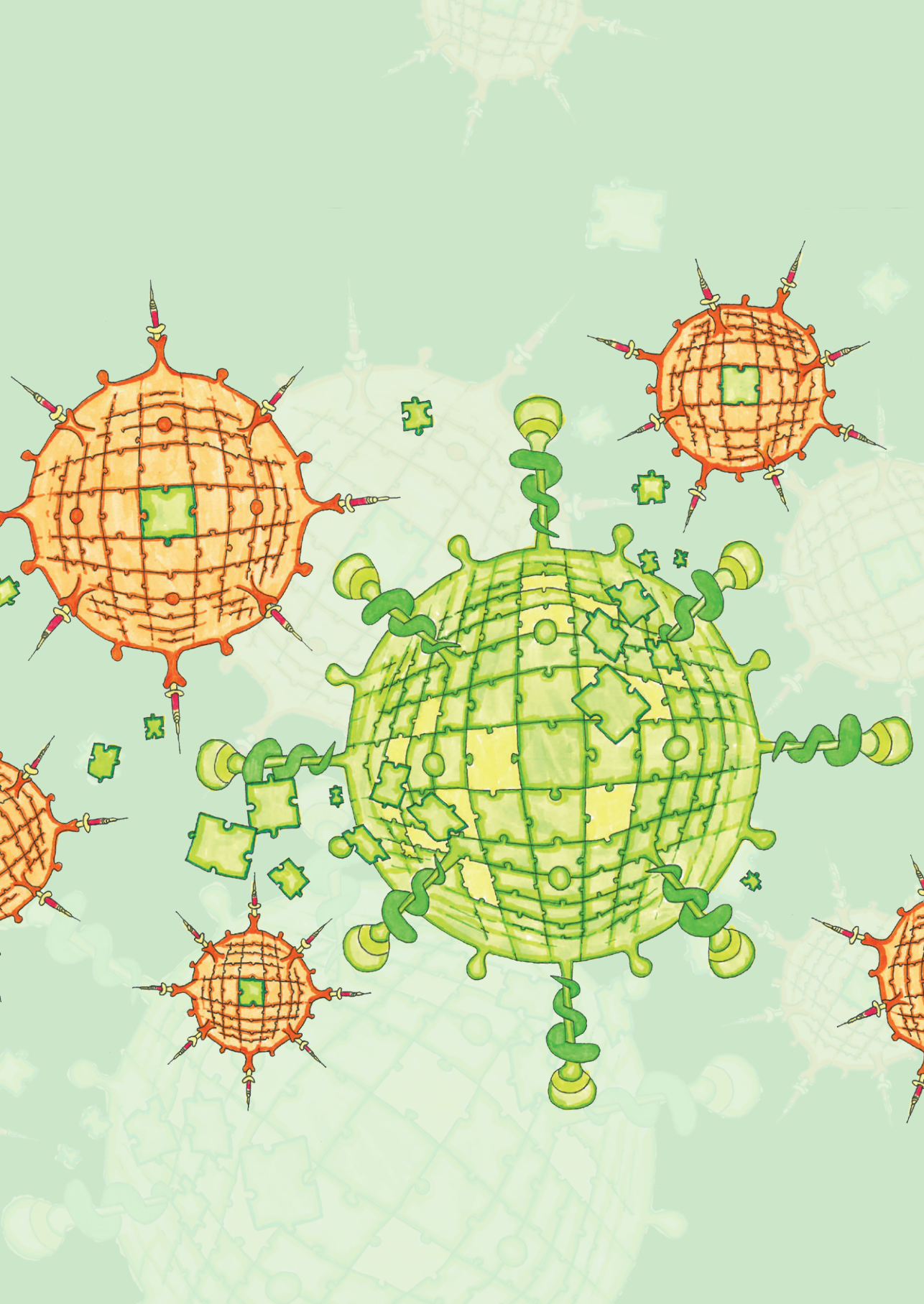
Variable	OR ^a	95%CI ^a	P	aOR ^a	95%CI ^a	P
Male sex	0.59	(0.54, 0.63)	<0.0001	0.70	(0.65, 0.76)	<0.0001
Age(y)	0.98	(0.97, 0.98)	<0.0001	0.98	(0.98, 0.98)	<0.0001
Migrant	1.62	(1.50, 1.76)	<0.0001	1.19	(1.09, 1.30)	0.00014
Addiction history	0.60	(0.54, 0.67)	<0.0001	0.73	(0.64, 0.82)	<0.0001
HIV	0.25	(0.21, 0.30)	<0.0001	0.30	(0.25, 0.37)	<0.0001
Cirrhosis	0.29	(0.22, 0.38)	<0.0001	0.38	(0.29, 0.51)	<0.0001
COPD	0.87	(0.67, 1.14)	0.32	1.44	(1.09, 1.91)	0.011
Diabetes	0.54	(0.41, 0.73)	<0.0001	0.72	(0.53, 0.97)	0.029
Malignancy	0.57	(0.48, 0.66)	<0.0001	0.77	(0.65, 0.91)	0.0022

^aOR = Odds ratio; CI = confidence interval; aOR = adjusted odds ratio

Table 5.2. Identification of variables contributing to HCU. Association between variables and severe suboptimal healthcare utilization within suboptimal HCU subgroup

Covariate	OR ^a	95%CI ^a	P	aOR ^a	95%CI ^a	P
Male sex	1.20	(1.06, 1.36)	0.0038	-	-	-
Age(y)	1.02	(1.02, 1.03)	<0.0001	1.02	(1.01, 1.02)	<0.0001
Migrant	0.64	(0.57, 0.73)	0.00066	0.79	(0.69, 0.91)	0.00066
Addiction history	1.35	(1.12, 1.63)	0.0020	-	-	-
HIV	6.20	(4.31, 8.92)	<0.0001	5.66	(3.91, 8.17)	<0.0001
Cirrhosis	1.25	(0.75, 2.09)	0.394	-	-	-
COPD	1.63	(1.09, 2.43)	0.017	-	-	-
Diabetes	1.06	(0.82, 1.77)	0.822	-	-	-
Malignancy	1.63	(1.26, 2.11)	0.00022	-	-	-

^aOR = Odds ratio; CI = confidence interval; aOR = adjusted odds ratio



Chapter 3

The impact of Hepatitis C Cure on Methadone Pharmacokinetics: A Case Series

Daan W. Von den Hoff

Elise J. Smolders

Floor A.C. Berden

David M. Burger

Solfrid Hegstad

Olav Spigset

Joost P.H. Drenth

Arnt F.A. Schellekens

Abstract

People who use drugs (PWUD) are at increased risk of chronic hepatitis C virus (HCV) infection and may also receive methadone as opioid agonist therapy (OAT). Multiple cytochrome P450 (CYP) enzymes, primarily found in the liver, seem involved in methadone metabolism (CYP3A4, CYP2B6, CYP2C9, CYP2C19, and CYP2D6). CYP3A4 is thought to be downregulated during infection or inflammation. Curing HCV might thus affect methadone plasma levels, potentially reducing effectiveness of methadone. This prospective case series explored the impact of HCV cure on methadone pharmacokinetics in patients receiving direct-acting antiviral therapy. Plasma samples were collected from four patients (age range 35-59) before start of HCV treatment and 12 weeks after completing treatment. Methadone levels were measured, and dose-normalized exposure was calculated. Two patients showed a decrease in plasma methadone levels of 23% and 26%, respectively, post treatment, and one of these required a dose increase due to reduced efficacy. These findings may suggest that HCV cure can lead to reduced methadone levels in some patients, potentially through the restoration of CYP3A4 activity, however the influence of other factors could not be excluded in this study.

Introduction

Most patients can be cured from HCV after two to three months of therapy with direct-acting antivirals (DAA). One of the remaining hepatitis C viral reservoirs is found among people who use(d) drugs (PWUD) [1]. PWUD often require long-term opioid agonist treatment (OAT) to counteract withdrawal and mitigate substance use related problems. OAT is mostly provided through methadone or buprenorphine formulations. About 33% of patients with opioid-related problems within Dutch addiction care is using methadone [2]. Hepatic impairment itself can alter the rate of drug metabolism [3]. Methadone metabolism can also be affected by liver cirrhosis; patients with moderate hepatic impairment (Child-Pugh B) have significantly higher systemic exposure to CYP3A4 substrates [4]. In addition, severe hepatic impairment (Child-Pugh C cirrhosis) prolongs the terminal half-life of methadone [5].

In addition to impaired liver function, there is evidence that hepatic inflammation itself can alter drug pharmacokinetics. Proinflammatory cytokines are believed to downregulate several drug-metabolizing enzymes, including CYP3A4 [6-9]. This suggests that HCV infection may suppress CYP3A4 activity. Consequently, following HCV cure, the restoration of CYP3A4 function could lead to increased metabolism of methadone, resulting in lower plasma levels, which have been shown to be correlated to withdrawal or craving symptoms [10].

The approved methadone hydrochloride tablets are a racemic mixture of two stereoisomers; R-Methadone is the pharmacologically active isomer responsible for reducing craving, and S-methadone retains other pharmacological effects; for example the antitussive activity [11]. Multiple cytochrome P450 (CYP) enzymes seem involved in its metabolism (CYP3A4, CYP2B6, CYP2C9, CYP2C19, and CYP2D6). Clinically relevant are mainly CYP3A4 and to a lesser extent CYP2D6 and CYP2B6 [12, 13].

The purpose of this study was to explore the impact of HCV clearance on methadone plasma levels. We hypothesized that curing HCV infection in PWUD on OAT decreases plasma methadone levels, potentially through restoring CYP3A4 activity.

Methods

Study Design

We conducted a prospective pharmacokinetic case series to explore the impact of HCV clearance on methadone plasma levels in PWUD. This case series was embedded within a Dutch national HCV-elimination program in addiction care [14]. The Research Ethics Committee Arnhem-Nijmegen has approved this study (reference number 2019-5939).

Study population

Eligible patients were HCV positive adults (≥ 18 years old) receiving racemic methadone treatment as opioid agonist therapy at the time of HCV treatment. Patients had to have reached an SVR at 12 weeks after completion of HCV treatment. The cohort was selected based on the availability and suitability of blood samples taken at baseline and at 12 weeks after HCV treatment.

Blood samples and plasma measurements

Blood samples were collected from patients at two key time points: (1) at baseline within three months before bore the initiation of DAA therapy, and (2) 12 weeks after the completion of the DAA treatment. These blood samplings were performed as part of regular hepatitis C care within the addiction treatment program. To measure methadone concentrations accurately, samples were drawn at least 4 hours after MET administration, and timing had to be consistent before and after DAA treatment for each patient, otherwise patients were excluded. Blood was obtained at local laboratories in EDTA tubes, within 48 hours plasma was separated by centrifugation, logged and stored at -80°C in department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands and in bulk transported on dry ice to the Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim Norway for the analysis of methadone. R/S-methadone was analyzed with an ultra-high performance supercritical fluid chromatography-tandem mass spectrometry (UHPSFC-MS/MS) method developed at the Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway as described previously [15]. In brief, sample preparation prior to analysis consisted of protein precipitation with acetonitrile and filtration through a phospholipid removal plate. The eluate was analyzed on an Acquity UPC2 system (Waters, Milford, MA, USA) coupled to a TQS-micro tandem mass spectrometry (Waters, Manchester, UK). Chromatographic separation was performed on a Chiralpak IH-3 (amylose-tris-[(S)- α -methylbenzylcarbamate], 2.1 mm $\times$ 150 mm, 3.0 μm particle size) from Chiralpak Technologies, Daicel group (Illkirch, France). The mobile phase consisted of CO_2 (A)

and 30mM ammonium acetate in methanol/water (98/2, v/v) (B). The calibration range was 50-1500 nM for each enantiomer and the between-assay relative standard deviations were in the range of 1.2–3.6%.

Study procedures

Within the Dutch HCV elimination program population, patients were invited to participate in this study and were asked for written informed consent [14]. We collected patient characteristics, addiction characteristics and history, substance use, medication use (if available), dose adjustments of methadone, treatment adherence, HCV RNA (as a measure for cure) and laboratory findings (i.e. ALT) from electronic patient files. Patient-reported craving was also collected. Data was recorded in CastorEDC without identifiable patient data by the local or coordinating investigator.

Study outcomes

The primary outcome was the change in dose normalized exposure (DNE), calculated by the change in plasma methadone before (timepoint 1) and twelve weeks after HCV treatment (timepoint 2), corrected for methadone dose.

Results

Four male patients were included (Table 1). At the time of HCV treatment initiation, methadone doses ranged from 30 mg/day to 112 mg/day. Dosing remained stable in two patients during HCV treatment, while one patient (patient no 1) tapered methadone and another (patient no 2) increased the dose based on an increase in craving. In all patients sampling took place at methadone steady state concentrations. There were no pharmacokinetic interactions between substances currently used by patients and methadone. In all patients, we assumed that concomitant drug use remained stable between methadone measurements. Methadone dosage, enantiomer concentrations, DNE, and ALT levels at the different timepoints are shown in Table 2.

Patient 1: The patient had significant somatic comorbidities, including chronic pulmonary disease and hearing loss of unspecified cause, and was diagnosed with lung cancer in early 2023. During HCV treatment, the patient remained on methadone maintenance therapy with a gradual taper from 112 mg/day to 68 mg/day (39% decrease), but was at steady state concentrations at both measurements. Despite ongoing use of alcohol, cocaine, and cannabis, no illicit opioid use or clinical destabilization was observed. Craving data was unavailable, but the patient remained psychiatrically stable throughout treatment. Total plasma concentration methadone

declined proportionally to the dose (both 39%) reduction, but interestingly, this patient showed an increase in R-methadone DNE and decrease in S-methadone DNE across measurements. ALT levels decreased from 63 to 40 U/L. These findings indicate that total methadone metabolism was not affected by HCV viral clearance or hepatic function restoration, but enantiomer metabolism might have been (Table 2).

Patient 2: The patient had comorbidities including a past disc herniation and recent gastrointestinal bacterial infection. During HCV treatment, the patient remained on methadone maintenance therapy, with the dose increased from 30 mg/day to 40 mg/day following reports of reduced subjective effect. Probably due to this increased methadone dose and continued heroin and cocaine use, there was no withdrawal or clinical destabilization. Craving data was unavailable. Plasma concentrations of S- and R-methadone showed minimal change despite the 33% dose increase, resulting in a 23% decrease in DNE, suggesting possible enhanced methadone clearance. Concurrently, ALT levels declined from 48 U/L to 24 U/L, indicating decreased hepatic inflammation.

Patient 3: The patient presented with complex psychosocial and medical challenges, limited cognitive functioning, and psychosis. During HCV treatment, the patient remained on a stable methadone dose of 90 mg/day without any adjustments. No illicit opioid or stimulant use was reported, and only occasional cannabis use occurred. Craving data was unavailable and psychiatric status remained stable under continued intramuscular depot olanzapine treatment (no interaction). Plasma concentrations of S- and R-methadone showed minimal variation (−5.4% and +2.6%, respectively), resulting in a negligible overall change in total exposure (−1.6%) and stable dose-normalized exposure, indicating steady plasma concentrations throughout treatment. ALT levels were in the normal range at timepoint 1 and unfortunately unavailable at timepoint 2.

Patient 4: He had cognitive impairment, chronic obstructive pulmonary disease, and recurrent lower respiratory tract infections. During HCV treatment, the patient remained on a stable methadone dose of 50 mg/day under inpatient supervision. The patient continued polysubstance use (Table 1), thus no withdrawal symptoms or changes in craving were reported, and psychiatric stability was maintained under ongoing oral olanzapine and valproic acid treatment (no interactions). Plasma concentrations of both S- and R-methadone declined by approximately 25%, resulting in a proportional 26% reduction in methadone DNE despite an unchanged methadone dose, suggesting increased methadone clearance. Concurrently, ALT levels decreased from 68 U/L to 26 U/L, consistent with hepatic improvement following HCV treatment.

Table 1. Patient overview

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	59	64	35	57
Origin	Dutch	Indonesian	Dutch	Dutch
Sex	Male	Male	Male	Male
Addiction history	Heroin, alcohol, cannabis, cocaine	Heroin, cocaine, cannabis	heroin, cannabis, amphetamines, alcohol	Heroin, GHB, amphetamines, alcohol, cannabis
Current substance use	Cocaine, alcohol, cannabis	Cocaine, heroin	Cannabis	Heroin, GHB, amphetamines, alcohol, cannabis
HCV treatment	Sofosbuvir/velpatasvir, 12 weeks	Sofosbuvir/velpatasvir, 12 weeks	Glecaprevir/pibrentasvir, 8 weeks	Glecaprevir/pibrentasvir, 8 weeks
Cirrhosis	absent	absent	absent	Child-Pugh A
Glomerular filtration rate (ml/min/1.73m²)*	>60	>60	>60	>60

* based on creatinine levels, sex and age; per 1,73 m2?

Table 2. Methadone dosage, concentration, dose normalized exposure (DNE)

Timepoint (T)	PATIENT 1			PATIENT 2			PATIENT 3			PATIENT 4		
	1	2	Change T1->T2	1	2	Change T1->T2	1	2	Change T1->T2	1	2	Change T1->T2
Methadone dose (mg)	112	68	-39%	30	40	33%	90	90	0%	50	50	0%
S-methadone (nM)*	638,2	314,6	-51%	251,9	262,7	4%	1306,3	1235,5	-5%	449	335,4	-25%
R-methadone (nM)	496,4	373,9	-25%	268,8	272	1%	1181,5	1211,6	3%	446,4	326,7	-27%
Total methadone (nM)	1134,6	688,5	-39%	520,7	534,7	3%	2487,8	2447,1	-2%	895,4	662,1	-26%
DNE S- methadone	5,7	4,6	-19%	8,4	6,6	-22%	14,5	13,7	-5%	9,0	6,7	-25%
DNE R-methadone	4,4	5,5	24%	9,0	6,8	-24%	13,1	13,5	3%	8,9	6,5	-27%
Total DNE methadone	10,1	10,1	0%	17,4	13,4	-23%	27,6	27,2	-2%	17,9	13,2	-26%
ALT (U/L)	63	40	-37%	48	24	-50%	17	-		68	26	-62%

* All methadone concentrations are given in nM. The conversion factor from nM to ng/mL is 0.31.

Discussion

In this study, two of four patients receiving methadone OAT demonstrated a marked reduction in methadone DNE following SVR after HCV treatment, whereas the other two showed stable DNE. These findings partially support our hypothesis that curing HCV infection in PWUD decreases plasma methadone levels. One possible explanation may be the influence of HCV on hepatic enzyme activity such as CYP3A4. Previous studies comparing healthy volunteers and HCV-infected patients showed reduced CYP3A4 activity, particularly affecting oral midazolam, which undergoes significant first-pass metabolism via CYP3A4 [9]. The metabolic AUC ratio of midazolam to α -hydroxy-midazolam dropped from 0.39 in healthy subjects to 0.25 in HCV treatment-naïve and 0.18 in HCV infected patients who failed treatment, indicating impaired conversion. This reduced CYP3A4 function also explains the need for higher tacrolimus doses during HCV therapy in some patients due to lower plasma concentrations [15]. Similar effects have been observed in other inflammatory states: voriconazole trough levels increased with CRP elevation in ICU patients, and CYP3A4 activity decreased by 61% during acute inflammation following orthopedic surgery [8, 16].

In our study, Patient 1 showed an increase in R-methadone and decrease in S-methadone concentrations after HCV clearance, resulting in an altered S/R ratio. Both isomers are equally metabolized by CYP3A4, but the S-enantiomer has more affinity for CYP2B6 compared to the R-enantiomer [17]. *In vitro* when CYP3A4 is inhibited, the predominant enantiomer is the S-metabolite probably to increased CYP2B6 metabolism. In our patient, before and after HCV clearance the S/R ratio was ~1.3 and 0.8, respectively, indicating that CYP2B6 became of lesser importance in methadone metabolism. This could fit our hypothesis that after HCV clearance CYP3A4 is upregulated and becomes the predominantly metabolizing enzyme again.

Methadone intrasubject metabolization variability is not a topic studied widely but may obscure identification of pharmacokinetic trends. For clearance the within subject variability was ≤ 2 fold for (R)-methadone whereas for (S)-methadone PK withinsubject variability was ~3.4 fold, larger 3 to 10 fold intersubject variability is reported [18, 19]. Several different processes may influence this variability possibly influencing our findings [20, 21]. Methadone undergoes complex, partly nonlinear kinetics influenced by variability in 1) absorption; 2) hepatic metabolism and 3) renal excretion, all causing variability. For example, bioavailability varies widely (41–95%) and 10–45% of the absorbed drug undergoes hepatic metabolism into inactive metabolites[22]. In addition, approximately 15–60% of the dose is renally

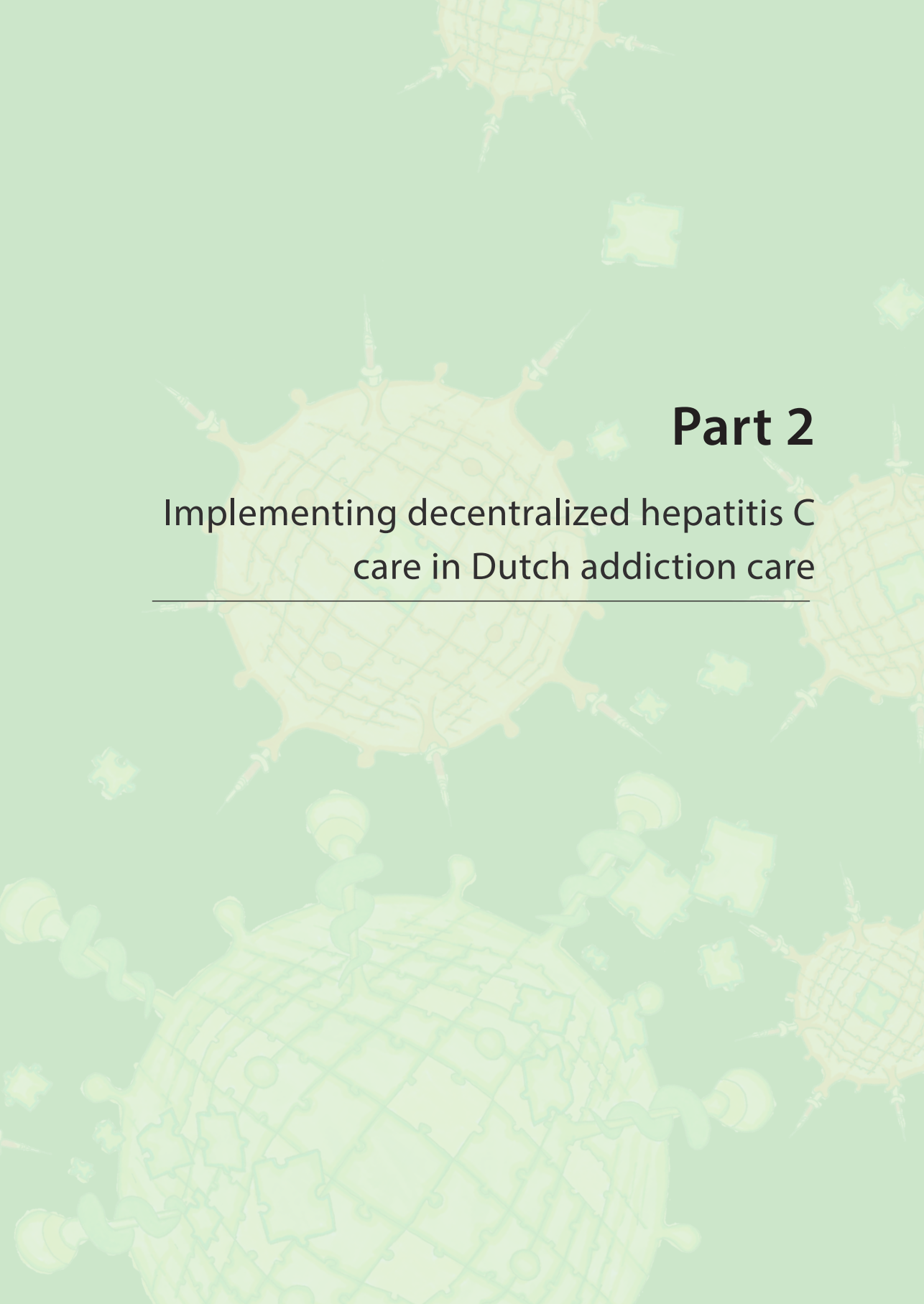
cleared, which is strongly dependent on urinary pH. Several other factors may also contribute to the variation such as protein binding and drug interactions [13]. A recent study found associations between the methadone concentration-to-dose ratio and body mass index, sex and a pharmacogenetic CYP2B6 genotype, but not age or degree of fibrosis [21]. In our study, the improvement in ALT after HCV treatment in several patients likely reflects reduced hepatic inflammation, yet uncontrolled and unmeasured factors probably play a role in the variability in methadone levels observed.

Taken together, our results suggest a possible trend toward reduced methadone exposure after HCV eradication, but conclusions remain tentative due to the small sample, unavailability of insights into other processes influencing metabolism, and absence of controlled pharmacokinetic assessment. To further assess the hypothesis we recommend a prospective, randomized bioequivalence study assessing full enantiomer-specific methadone pharmacokinetic profiles before and after HCV eradication under steady-state conditions. The suggested study should include stable methadone-maintained patients in which genotyping for CYP polymorphisms is available and all concomitant (illicit and prescribed) drug use and compliance is recorded. For clinical practice, a modest recommendation for awareness of potential decreases in methadone exposure during HCV treatment is warranted.

References

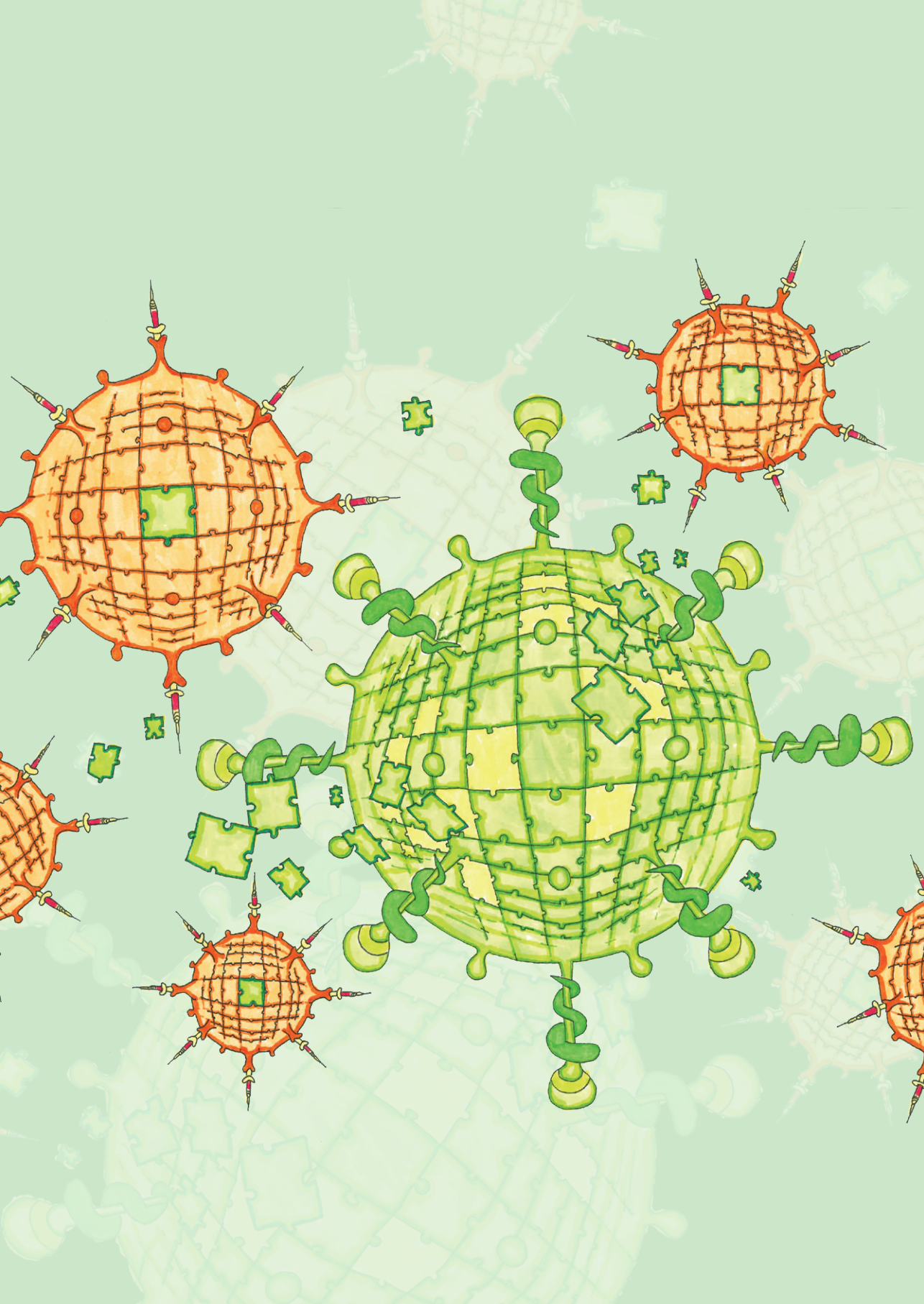
1. WHO, *Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030*. 2022.
2. Nationale Drug Monitor. *Opiaten 5.6 Hulpvraag en incidenten - Nationale Drug Monitor*. 2022 2 november 2022]; Available from: <https://www.nationaledrugmonitor.nl/opiaten-hulpvraag-en-incidenten/>.
3. Smolders, E.J., et al., *Pharmacokinetics, Efficacy, and Safety of Hepatitis C Virus Drugs in Patients with Liver and/or Renal Impairment*. *Drug Saf*, 2016. **39**(7): p. 589-611.
4. Abdallah, H. and M. Jerling, *Effect of hepatic impairment on the multiple-dose pharmacokinetics of ranolazine sustained-release tablets*. *J Clin Pharmacol*, 2005. **45**(7): p. 802-9.
5. Novick, D.M., et al., *Methadone disposition in patients with chronic liver disease*. *Clin Pharmacol Ther*, 1981. **30**(3): p. 353-62.
6. Veringa, A., et al., *Voriconazole metabolism is influenced by severe inflammation: a prospective study*. *J Antimicrob Chemother*, 2017. **72**(1): p. 261-267.
7. Christensen, H. and M. Hermann, *Immunological response as a source to variability in drug metabolism and transport*. *Front Pharmacol*, 2012. **3**: p. 8.
8. Encalada Ventura, M.A., et al., *Influence of inflammation on voriconazole metabolism*. *Antimicrob Agents Chemother*, 2015. **59**(5): p. 2942-3.
9. Morcos, P.N., et al., *Influence of chronic hepatitis C infection on cytochrome P450 3A4 activity using midazolam as an in vivo probe substrate*. *Eur J Clin Pharmacol*, 2013. **69**(10): p. 1777-84.
10. Dyer, K.R., et al., *Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: comparison of those who do and do not experience withdrawal and concentration-effect relationships*. *Clin Pharmacol Ther*, 1999. **65**(6): p. 685-94.
11. Ferrari, A., et al., *Methadone--metabolism, pharmacokinetics and interactions*. *Pharmacol Res*, 2004. **50**(6): p. 551-9.
12. Volpe, D.A., et al., *Methadone Metabolism and Drug-Drug Interactions: In Vitro and In Vivo Literature Review*. *J Pharm Sci*, 2018. **107**(12): p. 2983-2991.
13. B.V., S., *Methadon Summary of Product Characteristics*. 2024.
14. Von den Hoff, D.W., et al., *Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care. Study protocol for the Hepatitis C: chain of addiction care (CAC) project*. *Addict Sci Clin Pract*, 2022. **17**(1): p. 67.
15. Smolders, E.J., et al., *Decreased tacrolimus plasma concentrations during HCV therapy: a drug-drug interaction or is there an alternative explanation?* *Int J Antimicrob Agents*, 2017. **49**(3): p. 379-382.
16. Lenoir, C., et al., *Impact of Acute Inflammation on Cytochromes P450 Activity Assessed by the Geneva Cocktail*. *Clin Pharmacol Ther*, 2021. **109**(6): p. 1668-1676.
17. Chang, Y., et al., *Stereo-selective metabolism of methadone by human liver microsomes and cDNA-expressed cytochrome P450s: a reconciliation*. *Basic Clin Pharmacol Toxicol*, 2011. **108**(1): p. 55-62.
18. Eap, C.B., *Interindividual Variability of the Clinical Pharmacokinetics of Methadone*. *Clinical Pharmacokinetics*, 2012. **Volume 41**.
19. Hanna, J., et al., *Within- and between- subject variability in methadone pharmacokinetics and pharmacodynamics in methadone maintenance subjects*. *Br J Clin Pharmacol*, 2005. **60**(4): p. 404-13.
20. Eap, C.B., T. Buclin, and P. Baumann, *Interindividual Variability of the Clinical Pharmacokinetics of Methadone*. *Clinical Pharmacokinetics*, 2002. **41**(14): p. 1153-1193.

21. Chalabianloo, F., et al., *Methadone pharmacokinetics in opioid agonist treatment: Influencing factors and clinical implications*. Basic Clin Pharmacol Toxicol, 2024. **134**(3): p. 333-344.
22. Nilsson, M.I., U. Meresaar, and E. Anggard, *Clinical pharmacokinetics of methadone*. Acta Anaesthesiol Scand Suppl, 1982. **74**: p. 66-9.



Part 2

Implementing decentralized hepatitis C care in Dutch addiction care



Chapter 4

Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care. Study protocol for the Hepatitis C: chain of addiction care (CAC) project

Daan W. Von den Hoff

Floor A. C. Berden

Joost P. H. Drenth

Arnt F. A. Schellekens on behalf of HepNed and NISPA

Abstract

Background: People who use drugs (PWUD) are at high risk for hepatitis C virus (HCV) infection and its complications. Given the high prevalence rate of HCV in PWUD, the World Health Organization (WHO) emphasizes PWUD as a target population for HCV elimination. The introduction of pangenotypic direct acting antivirals (DAAs) greatly simplifies HCV treatment, which encourages integration of HCV treatment in primary care. Facilitating low threshold HCV care for PWUD by implementing decentralized models is crucial for HCV elimination.

Aims: With this study we aim to 1) eliminate 90% of identified HCV infections in Dutch addiction care, using a decentralized PWUD-HCV care model, and 2) identify facilitators and barriers for successful implementation of the model using interviews.

Methods: We will perform a multicenter mixed-method study on HCV treatment in addiction care. In a prospective observational study we will examine HCV-related outcomes in PWUD receiving HCV treatment as part of addiction care. The primary outcome is viral elimination, defined as percentage of identified HCV positive patients cured with DAAs. In parallel, we will perform a qualitative study to explore facilitators and barriers for implementation of fully decentralized HCV-PWUD care. We will interview addiction care professionals and board members about their experience with HCV-care as part of addiction care.

Discussion: This study will show effectiveness of integration of HCV care within addiction care, and provide insight in facilitators and barriers to implement integrated HCV-addiction care. The results will provide recommendations for implementation and maintenance of the decentralized HCV pathway, which can facilitate scaling-up to contribute to reaching WHO HCV elimination goals.

Trial registration: NCT05401136

Introduction

The World Health Organization has set ambitious goals to eliminate hepatitis C virus (HCV) as a public health threat, aiming at a 90% reduction of new HCV infections and a 65% reduction of HCV related mortality (1, 2). Disease progression models indicate only 24% of high-income countries are on track for achieving these goals before 2030 at the current rate of diagnosis and treatment (3, 4). Expansion of efforts is therefore required.

One paramount strategy to reach HCV elimination goals is micro-elimination in specific target populations where HCV is prevalent, such as people who use drugs (PWUD). An estimated ~3,400 HCV RNA positive former and current injecting drug users remain in the Netherlands, despite availability of free HCV care across the country (5). Injecting drug users are a subpopulation of PWUD and prevalence in the total Dutch PWUD population is currently unknown.

Studies indicate that HCV-infected PWUD may frequently get lost in the HCV care chain from diagnosis, to initiation of treatment and follow-up (6). Recent studies showed that a median of 50% of PWUD with HCV visit the HCV specialist after testing positive and subsequently only 53% of those initiate treatment (7). Loss to follow up during (median 2.5%) and after treatment (median 7.1%) were comparable to the general population (7). Between 2013 and 2016 the Dutch HCV standard of care in addiction centers was evaluated and improved. Although major strides were made, linkage to hospital care and treatment remained as significant barriers due to DAA restrictions (8).

Over the past decade, DAA therapy became widely available and is now standard care globally. Recently, the use of pangenotypic DAAs, which bypass genotyping and simplify therapy choice, were recommended by both American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) (9, 10). Furthermore, evaluation of liver fibrosis can be done using non-invasive, inexpensive and reliable biomarker panels, further reducing complexity of HCV care and burden for patients (10). As a result, initiatives to offer decentralized HCV care for PWUD have been studied. A recent meta-analysis showed increasing linkage to care, with increasing levels of decentralization (11). With full decentralization, HCV testing and treatment at the same site, showed the highest linkage to care of 72%, whereas without decentralization this was only 47%. Treatment uptake rate showed similar results (11). Successful implementation of decentralized pathways are therefore the next step in achieving HCV elimination in PWUD (12, 13).

Previous studies have examined challenges in implementation of HCV care for PWUD outside of the hospital care setting (14-17). Linkage to HCV care in PWUD may be reduced as a result of poor venous access due to damaging effects of intravenous drug use which precludes laboratory monitoring of treatment. A recent qualitative telephone interview study in general practitioners who prescribe opioid agonist therapy and addiction care specialists also identified logistic barriers like lack of testing on-site, and difficulty in liver fibrosis assessment (18). There remains a need for addiction care focused research emphasizing residual local barriers, for instance stigmatization and lack of support for task shifting at management level. Nurses also play a vital role in addiction care, their perspectives are lacking in literature.

Dutch addiction care is provided through an integrated trajectory and joins government, municipality, justice system and health service providers with common goals of public order as well as public health and quality of care and treatment. Addiction care centers are a part of mental healthcare and deliver care that targets specific populations, provide outreach, night shelters, outpatient- and inpatient addiction treatment facilities. In addition, these institutions provide and coordinate reintegration projects, daytime activities, education and harm reduction (i.e. needle exchange programs).(19)

We aim to evaluate the effectiveness and feasibility of the HCV: Chain of Addiction Care project, which decentralizes HCV care in Dutch addiction care. This mixed-method study consists of 1) an observational study to explore its effectiveness in achieving 90% hepatitis C elimination, and 2) a qualitative study to explore facilitators and barriers for its implementation.

Methods

Study design

This mixed-method study consists of two parts. Part 1 is a multi-center observational cohort study that will study the effectiveness of the structured implementation of CAC in a PWUD population receiving addiction care. Part 2 is a qualitative study using semi-structured interviews regarding addiction care professionals' personal perspective on barriers and facilitators for implementation of the CAC pathway. We will focus on addiction care specialists and nurses, as well as board members in addiction care as all play a vital role in successful implementation of decentralization projects. The interviews will either take place face-to-face or digitally using a

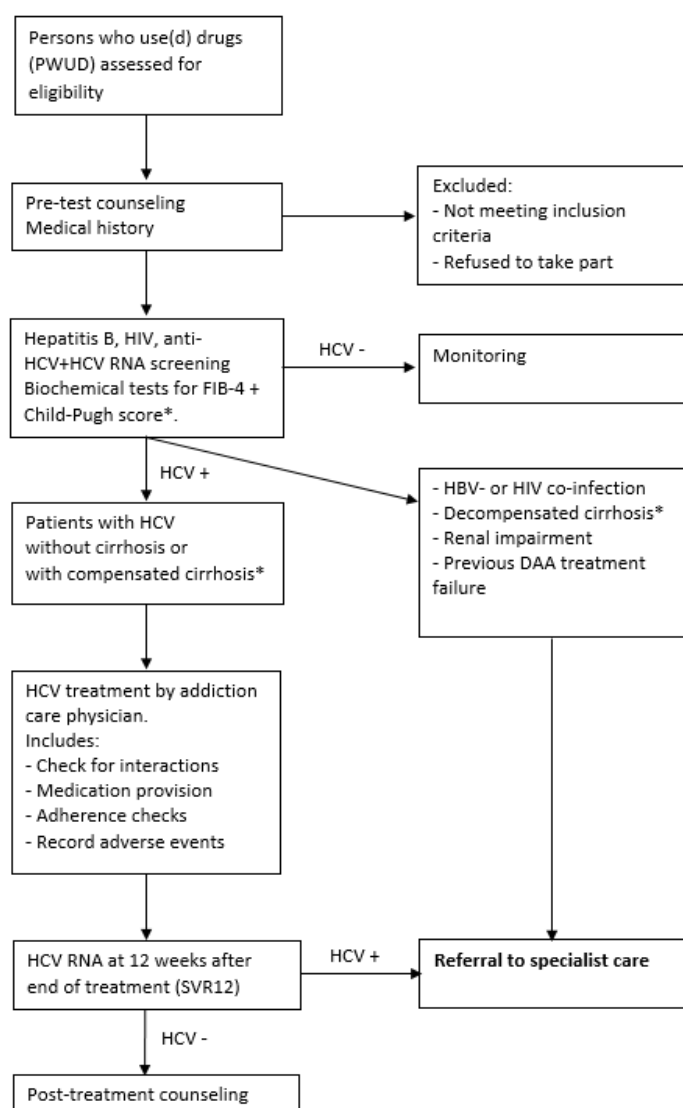
videoconferencing platform. The interviews will be audio recorded and transcribed verbatim. The mixed-method design will be integrated into the RE-AIM framework to allow for evaluation using a well-established method for implementing community-based health interventions. The RE-AIM framework facilitates the translation of research to practice with attention for contextual factors, as opposed to only efficacy or effectiveness (20). RE-AIM involves evaluation in five dimensions (Reach, Effectiveness, Adoption, Implementation, Maintenance), resulting in a more explicit description of the strategy. RE-AIM has been used extensively in over 450 publications on study planning or intervention evaluation (21).

The Chain of Addiction Care (CAC) project

The CAC pathway is a new approach to HCV care in the Dutch addiction care setting, in line with regular HCV care guidelines (9, 10). All five addiction care organizations in the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA) collaboration will be invited to participate but we will also reach out to other major addiction care organizations to achieve nationwide coverage. All centers will be invited within a timeframe of two months. There will be no financial compensation for participation, however participation will include free education on hepatitis C. We anticipate that at least four out of five NISPA organizations and at least two non-NISPA organizations will participate. We will focus on centers that provide outpatient care, outreaching care or methadone posts, as these settings will contain most patients at risk for bloodborne infections and be suitable to provide hepatitis C care. Unfortunately, inpatient hepatitis C treatment is not currently reimbursed in the Netherlands. All phases of HCV care tasks are shifted to the addiction care physicians (ACP) and nurses, from case finding in patients with a risk for bloodborne infections to counseling, testing, treatment and follow-up. Patients at risk who visit the participating centers will be educated on viral hepatitis and HIV and motivated to undergo venipuncture. In the majority of patients, pangenotypic DAA treatment will be provided by the ACP after evaluation of biomarker panels (Figure 1).

CAC is a project that is part of the portfolio that is offered by HepNed, a collaboration between hepatologists and infectious disease physicians. HepNed coordinated the nationwide hepatitis C retrieval program CELINE (22). During the CAC project, as addiction care teams are familiarized with HCV care, a HepNed expert is available for advice and instruction. In some cases treatment provided by a viral hepatitis expert is preferred: in patients with co-infection hepatitis B or HIV, renal impairment (eGFR <30ml/min/1.73m²) and in patients who previously failed DAA therapy or patients who present with decompensated cirrhosis (Child-Pugh B and C). In case of advanced fibrosis or compensated cirrhosis (Fib-4 > 3,25 and Child-Pugh A),

patients receive hepatitis C treatment in addiction care and are simultaneously referred for fibrosis analysis and cirrhosis follow-up in secondary care. Patients who fail treatment will be referred to specialist care. After completing the treatment, patients will be counseled and reintroduced into established health screening programs. Patients with an HCV reinfection will be treated as new patients and can be treated on-site again.



*decompensated cirrhosis as indicated by FIB-4 score (>3.25) and Child-Pugh score B or C; compensated cirrhosis as indicated by FIB-4 score (>3.25) and Child-Pugh score A.

Figure 1: CAC flowchart

Implementation requires a dynamic and tailored approach to the local situation in the individual addiction care center based on variation in availability of on-site venipuncture, outreaching healthcare providers and existing collaborations with viral hepatitis experts. Derived from barriers found in previous studies, CAC interventions include DAA provision in methadone distribution posts and a limit to excess blood withdrawals by testing in combination with health screenings and implementation of reflex HCV-RNA testing.

Study population

In Part 1 addiction care physicians will invite consecutive people who inject(ed) drugs or have other risk factors for HCV infection and who visit the CAC addiction care centers to participate. In order to be eligible for this study, a subject must be aged 18 years or older and able and willing to give informed consent. For the duration of the project, as many patients as possible will be included. There are no exclusion criteria for this study. Patients will be followed-up until the end of their HCV care journey. Since the CAC pathway is standard care in a decentralized setting, no comparison group can be formed. In part 2 we will invite addiction care physicians, nurses and addiction care policy makers employed both in centers participating in CAC and centers that do not.

Study outcomes

The primary outcome in part 1 is HCV viral elimination, defined as percentage of patients that achieved SVR among identified HCV RNA positive patients. Secondary outcomes are total number of patients tested, prevalence of HCV antibody and RNA positivity among tested patients, fibrosis stage in HCV positive patients as found by FIB-4 and/or Child-Pugh scores, decentralized treatment initiation rate, treatment completion, sustained virologic response rate and referral. The main study outcomes for part 2 are the barriers and facilitators contributing to (un)successful implementation of the HCV care pathway for PWUD in the Netherlands.

Data collection and management

The main study parameters collected are: acceptance rate of (on-site) testing, HCV prevalence, treatment acceptance rate, sustained virologic response (SVR) rates and re-infection rates. Furthermore, we will collect data on patient characteristics such as sex, age, history of drug use, medical history and comorbidities (including previous HCV infection and treatment), concomitant medication and available HCV-related clinical data (e.g. other risk factors, blood test results, liver fibrosis stage). All these parameters are stored in the electronic patient files by the patient's treatment team as part of standard care. Data will then be collected anonymously

by a member of the research staff according to the medical code of conduct (23). A validated and GCP compliant data management program, CastorEDC, will be used for central data storage.

Interview recordings in part 2 of the study will be anonymized and used solely by the researchers. The interview guide will address the following topics: preferred role of addiction center in HCV care: specifically for diagnosis, treatment and follow-up; experience and viewpoint on fully decentralized HCV care; real and anticipated barriers and facilitators for successful and sustainable implementation. Interviewee data collected includes participant characteristics such as sex, age, occupation and years of experience.

Analysis

For the quantitative study (part 1) we will use descriptive statistics. Primary and secondary endpoints, as well as baseline patient characteristics will be presented as percentages, means ($\pm$ SD) or medians (IQR), depending on the variable and its distribution. No sample size is recorded as this is an observational prospective cohort study without a comparison group. All analyses will be performed using the statistical package SPSS, version 25.0 (SPSS Inc. Chicago, IL, USA).

In the qualitative study (part 2), Braun and Clarke's approach to thematic analysis will be used to identify common themes across the interview transcripts (24). The analysis will involve a six-phase process: familiarization with the transcripts, coding, searching for themes, reviewing themes, defining and naming themes and writing. The coding process will be data driven, in which codification is performed following an inductive method and themes are constructed from the data. Each transcript will be coded in pairs of 2 researchers. Qualitative thematic analysis will be performed using ATLAS.ti v9.1.6.

Ethics

The Research Ethics Committee Arnhem-Nijmegen has waived formal ethical approval for this study, indicating it is not included in the Medical Research Involving Human Subjects Act. Eligible patients will be informed about the study by a member of the treatment team in the standard care pathway. While regular care continues as planned, patients are given sufficient time to consider participation in the study. Informed consent will be obtained before the collection of data by the coordinating researchers. Patients will be followed-up until the end of this study or until they withdraw consent. Due to the observational character of this study, participation poses no burden or risk for the participants. Participation leads to

evaluation and may lead to improvement of the hepatitis care in addiction care facilities in the future, which benefits patients. Patients who decline participation in this study will still be offered access to onsite HCV care if the addiction care team can provide it.

Discussion

HCV viral elimination in line with WHO goals is within reach (4). Micro-elimination efforts in target populations like PWUD are essential in countries with a low HCV prevalence in the general population like the Netherlands. This study aims to test a decentralization model tailored to population and system needs, aimed to integrate HCV care within addiction care, with the specific objectives to 1) test effectiveness in achieving 90% elimination viral elimination rates; and 2) explore facilitators and barriers for implementation of decentralized HCV care within addiction care.

Efficient, low-threshold treatment for HCV-infected PWUD is one strategy of HCV-micro-elimination to reduce the human reservoir of HCV and contribute to HCV elimination goals of the WHO(25). The findings of this study will strengthen the evidence base for decentralized HCV-care within addiction care. Furthermore, identification of facilitators and barriers for implementation of a decentralized HCV-care model within addiction care can identify best practices and feed into a blueprint to support scaling-up of HCV care decentralization. Thus, the current study will contribute to achieving WHO HCV elimination goals.

We make use of the RE-AIM framework to systematically evaluate all necessary dimensions for successful implementation of decentralized HCV care. It has to be acknowledged that commonly not all dimensions of the RE-AIM framework are covered within a single study. This also applies to the current study, where research objective one provides information on both reach and effectiveness of the intervention in real life, and the qualitative research objective two will mainly provide information on implementation (see Table 1). If successful, future studies should explore maintenance of decentralized HCV care within addiction care.

This study has multiple strengths. First, its nationwide implementation in different addiction care settings will ensure a heterogenic PWUD study population, increasing generalizability of findings. This allows us to translate our results to other addiction care facilities both in the Netherlands and other countries. Second, the mixed method design of this study allows for observational outcomes to be

substantiated by qualitative findings that provide more in-depth information and understanding of the quantitative observations. Lastly, CAC efforts are guided by an experienced interdisciplinary team of behavioral scientists, addiction care experts, and viral hepatitis experts through HepNed. This will grant a unique opportunity to bridge the gap between addiction care and hospital care.

Table 1. Methods and endpoints in the RE-AIM framework

Quantative study endpoints: HCV care pathway (part 1)	RE-AIM dimension*	Qualitative study endpoints: barriers and facilitators (part 2)
Demographics of population	<i>Reach</i>	Individual reasons for not participating.
Proportion of population tested.		Recruitment of patients
		Willingness to participate
Viral elimination rate	<i>Effectiveness</i>	-
Proportion of centers participating	<i>Adoption</i>	Willingness to initiate the program
Secondary HCV care endpoints (treatment uptake, completion)	<i>Implementation</i>	Strategies to improve implementation.
Referral to hospital		
Loss to follow up		
Adherence		

*Maintenance is beyond the scope of this study but will be the focus of future studies.

A limitation of this study is the lack of a control group, as the CAC pathway utilizes standard of care treatment. Also, we believe it would be unethical to deny patients in a control group safe and effective decentralized treatment, given the current evidence for decentralization of HCV care. Another limitation is that the ‘maintenance’ dimension of the RE-AIM model is beyond the scope of the study. The timeframe for this study does not include long-term follow-up. However, we do aim to establish low threshold communication between local hospitals and participating addiction care centers to fully integrate decentralized HCV care in the long-term. We therefore suggest evaluating the long-term effect and adherence to implemented decentralized care models in future studies. Finally, it is important to note that not all PWUD seek care. In a field work study conducted in 2013, of 401 problematic opioid users (regular use with either criminal activity, comorbid psychiatry, or unstable lifestyle) 79.2% reported to have received addiction care in 2012. Based on this finding they estimated the size of the problematic opioid user population in the Netherlands at 14,000, a decline of 21% compared to 2009 (26). Trends of problematic opioid use in addiction care in the Netherlands has since declined further, also their average age continues to rise, which indicates

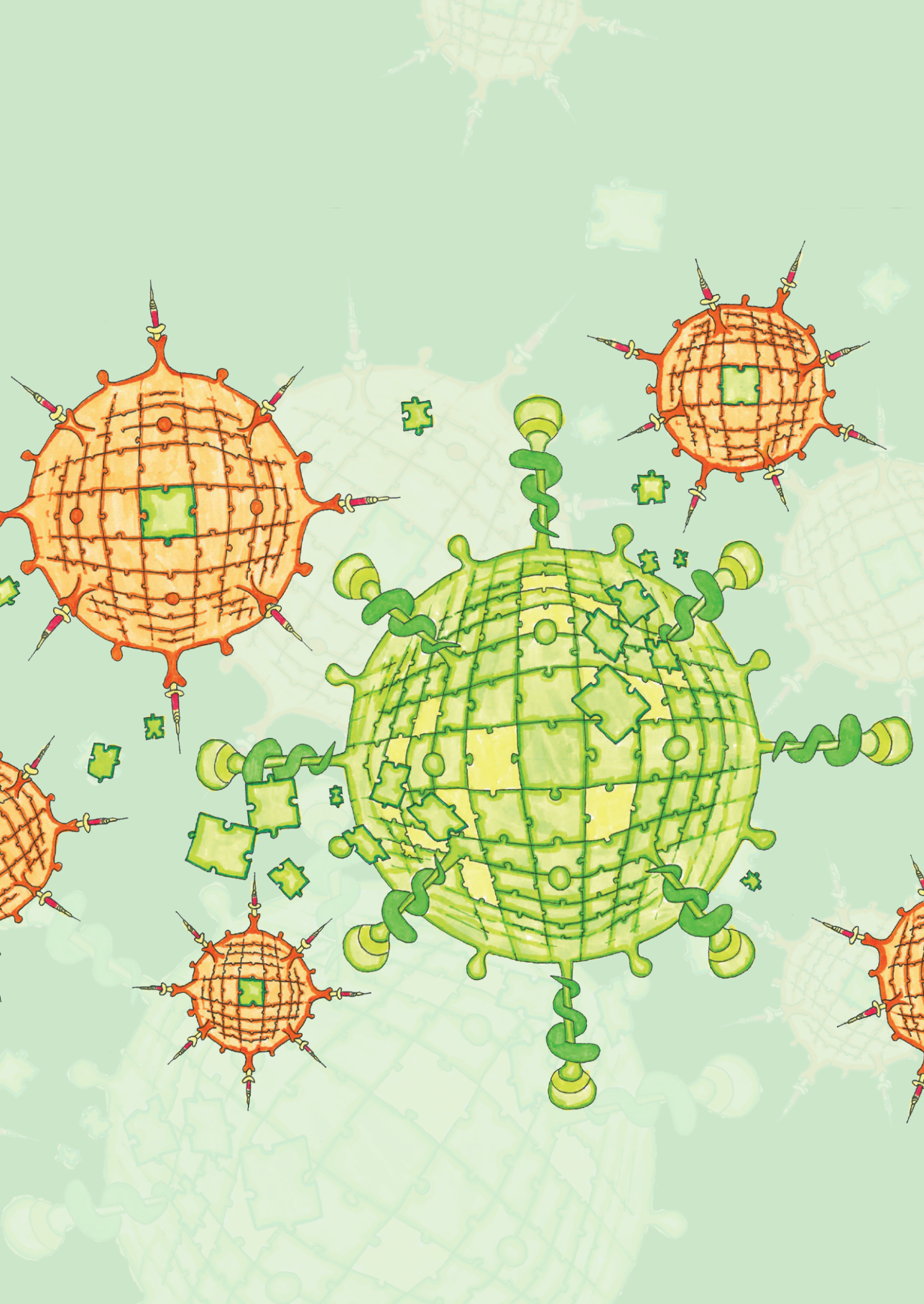
a minimal influx of new patients (27). This means that there is a treatment gap, potentially hindering the reach of our intervention. However, given these findings our intervention within addiction care would still reach the majority of our target population.

To summarize, we will describe the nationwide implementation of CAC, a decentralized HCV care model for PWUD in the Netherlands. The study is aligned along the RE-AIM framework, aiming to contribute to HCV elimination among PWUD. Using a mixed methods approach, this study will substantiate current evidence for fully decentralized HCV-care, integrated in addiction care, and provide insights in potential facilitators and barriers for implementation and scaling-up of this decentralized HCV-treatment approach. This will contribute to achieving WHO hepatitis C elimination goals worldwide.

References

1. WHO. Combating hepatitis B and C to reach elimination by 2030. Geneva, Switzerland: WHO. 2016.
2. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. *The Lancet*. 2019;394(10207):1451-66.
3. Gamkrelidze I, Pawlotsky JM, Lazarus JV, Feld JJ, Zeuzem S, Bao Y, et al. Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. *Liver Int*. 2021;41(3):456-63.
4. van Dijk M, Brakenhoff SM, Isfordink CJ, Cheng WH, Blokzijl H, Boland G, et al. The Netherlands Is on Track to Meet the World Health Organization Hepatitis C Elimination Targets by 2030. *J Clin Med*. 2021;10(19).
5. Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. *Epidemiol Infect*. 2019;147:e147.
6. Grebely J, Oser M, Taylor LE, Dore GJ. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. *J Infect Dis*. 2013;207 Suppl 1:S19-25.
7. van Dijk M, Drenth JPH, HepNed study g. Loss to follow-up in the hepatitis C care cascade: A substantial problem but opportunity for micro-elimination. *J Viral Hepat*. 2020;27(12):1270-83.
8. Kracht PAM, de Gee EA, van der Poel A, Verhagen M, Hoepelman AIM, Croes EA, et al. Introducing hepatitis C virus healthcare pathways in addiction care in the Netherlands with a Breakthrough project: a mixed method study. *Harm Reduct J*. 2019;16(1):45.
9. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology*. 2020;71(2):686-721.
10. EASL eee, Clinical Practice Guidelines Panel C, representative EGB, Panel m. EASL recommendations on treatment of hepatitis C: Final update of the series(). *J Hepatol*. 2020;73(5):1170-218.
11. Oru E, Trickey A, Shirali R, Kanter S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health*. 2021;9(4):e431-e45.
12. Von den Hoff DW, Berden FAC, Schellekens AFA. If the mountain won't come to Mohammed, then Mohammed must go to the mountain: Decentralisation of hepatitis C care for people who use drugs. *United European Gastroenterol J*. 2021.
13. Mangia A, Rina MF, Canosa A, Piazzolla V, Squillante MM, Agostinacchio E, et al. Increased Hepatitis C virus screening, diagnosis and linkage to care rates among people who use drugs through a patient-centered program from Italy. *United European Gastroenterol J*. 2021;9(10):1109-18.
14. Assoumou SA, Sian CR, Gebel CM, Linas BP, Samet JH, Bernstein JA. Patients at a drug detoxification center share perspectives on how to increase hepatitis C treatment uptake: A qualitative study. *Drug Alcohol Depend*. 2021;220:108526.
15. Litwin AH, Drolet M, Nwankwo C, Torrens M, Kastelic A, Walcher S, et al. Perceived barriers related to testing, management and treatment of HCV infection among physicians prescribing opioid agonist therapy: The C-SCOPE Study. *J Viral Hepat*. 2019;26(9):1094-104.
16. Phillips C, Schulkind J, O'Sullivan M, Edelman N, Smith HE, Verma S, et al. Improving access to care for people who inject drugs: Qualitative evaluation of project ITTREAT-An integrated community hepatitis C service. *J Viral Hepat*. 2020;27(2):176-87.

17. Tsui JI, Barry MP, Austin EJ, Sweek EW, Tung E, Hansen RN, et al. 'Treat my whole person, not just my condition': qualitative explorations of hepatitis C care delivery preferences among people who inject drugs. *Addict Sci Clin Pract.* 2021;16(1):52.
18. Marshall AD, Grebely J, Dore GJ, Treloar C. Barriers and facilitators to engaging in hepatitis C management and DAA therapy among general practitioners and drug and alcohol specialists- The practitioner experience. *Drug Alcohol Depend.* 2020;206:107705.
19. Schatz E. IDPC Briefing Paper The Dutch treatment and social support system for drug users. International Drug Policy Consortium. 2011.
20. Sweet SN, Ginis KA, Estabrooks PA, Latimer-Cheung AE. Operationalizing the RE-AIM framework to evaluate the impact of multi-sector partnerships. *Implement Sci.* 2014;9:74.
21. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. *Front Public Health.* 2019;7:64.
22. Isfordink CJ, van Dijk M, Brakenhoff SM, Kracht PAM, Arends JE, de Kneegt RJ, et al. Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination. *Eur J Intern Med.* 2022.
23. Federation of Dutch Medical Scientific Societies; The code of conduct for the use of data in health research 2004.
24. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology.* 2006;3(2):77-101.
25. WHO. Report WHO Global health sector strategy on viral hepatitis. Geneva, 2017.
26. Cruts G VLM, Buster M. . Aantal en kenmerken van problematische opiatengebruikers in Nederland. Utrecht/Amsterdam: Trimbos-instituut/GGD Amsterdam. 2013.
27. Nationale Drug Monitor. Opiaten 5.6 Hulpvraag en incidenten - Nationale Drug Monitor: Trimbos-instituut, Utrecht & WODC, Den Haag; 2022 [Available from: <https://www.nationaledrugmonitor.nl/opiaten-hulpvraag-en-incidenten/>].



Chapter 5

Successful hepatitis C elimination through decentralized treatment in Dutch addiction care: a RE-AIM based evaluation

Daan W. Von den Hoff
Floor A.C. Berden
Annemarie Noordeloos
Thomas Knuijver
Arnt F.A. Schellekens
Joost P.H. Drenth

Abstract

Background: People who use drugs (PWUD) are an important population of focus for hepatitis C virus (HCV) elimination. Case-finding and treatment of these patients in outpatient specialist care is a challenge due to population specific barriers. Screening and treatment integrated in addiction care might overcome these barriers. With this study we aim to evaluate the implementation of a decentralized PWUD-HCV care model.

Methods: We conducted a multicenter prospective observational study in Dutch addiction care centers to assess a decentralized HCV care pathway for PWUD. Implementation of HCV-care within addiction care was evaluated using the Reach-Effectiveness-Adoption-Implementation-Maintenance (RE-AIM) framework. Viral elimination, defined as the proportion of identified HCV-RNA positive PWUD achieving sustained virologic response (SVR), was the primary outcome.

Results: Reach: 870 anti-HCV tests were performed, 29 HCV-RNA positive PWUD were enrolled. Effectiveness: 23 patients initiated and completed on-site treatment, three patients were referred for treatment, two patients were lost to follow-up and one patient refused treatment. All patients tested for SVR achieved SVR, one patient was lost to follow-up before SVR test. The elimination rate was 86% (25/29). Adoption: five out of eleven addiction care organizations (45%) implemented decentralized HCV care within addiction care. Implementation fidelity was high.

Conclusion: This study demonstrates that successfully implemented decentralized HCV care within addiction services is feasible and highly effective, achieving an elimination rate of 86%. However, adoption of decentralized HCV care was limited, underscoring the need for targeted strategies to enhance implementation. Our findings support expanding of decentralized HCV care models in addiction settings to meet HCV elimination targets.

Trial registration: NCT05401136

Introduction

The World Health Organization (WHO) aims to eliminate hepatitis C virus (HCV) as a significant public health challenge by 2030. Targets include reducing new HCV infections by 90% and HCV-related mortality by 65% (1, 2). However, modeling studies reveal that only 24% of high-income nations are likely to achieve these goals without accelerating current rates of diagnosis and treatment (3, 4). More recent estimates show that global progress has been uneven and will need to accelerate considerably to reach the WHO's 2030 goals (5, 6). Consequently, intensified interventions are necessary to close this gap. One key approach is micro-elimination, focusing on specific groups with increased HCV prevalence (7, 8).

A population of focus for HCV micro-elimination are people who use drugs (PWUD). In the Netherlands, the prevalence of chronic HCV infection in people injecting drugs is estimated between 35% and 83%, translating in ~ 3400 cases in 2019, despite nationwide access to reimbursed Direct-Acting-Antiviral (DAA) therapy (9). A recent review found that only half of PWUD diagnosed with HCV, had consulted with an HCV specialist, and just 53% of those had initiated treatment (10). Loss to follow-up rates during (2.5% median) and after treatment (7.1% median) are comparable to those observed in the general population (10, 11).

HCV care is often delivered in specialized outpatient clinics, creating barriers for PWUD with HCV infection (12-16). The discovery of DAA which allows short [8-12 weeks], simplified and highly effective treatment has made options for HCV cure widely accessible (17). Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have recommended the use of pangenotypic DAAs, non-invasive and cost-effective liver fibrosis assessments, and streamlined care pathways to lower the HCV treatment burden (17, 18).

As a corollary decentralized management of HCV has become a viable option. In this study, decentralized HCV care refers to the delivery of hepatitis C testing, evaluation, and treatment in non-specialist, community-based settings (e.g., addiction care, primary care, or outreach services), rather than exclusively within hospital-based specialist clinics. Various decentralized care models tailored to PWUD have been explored, offering testing and treatment in addiction care (19-24).

In the Netherlands, addiction care is organized through a nationwide network of regional centers. These services are fully reimbursed and are accessible to all individuals upon referral, typically by general practitioners. Addiction care centers deliver a

comprehensive package of services, including prevention, harm reduction (such as needle and syringe programs), and addiction treatment. This system plays a critical role in addressing the needs PWUD and contributes significantly to public health (25).

Between 2013 and 2016 the Dutch HCV standard of care in addiction centers was evaluated and improved. Although major strides were made, linkage to hospital care and treatment remained as significant barriers due to DAA restrictions (26). We initiated the Hepatitis C Chain of Addiction Care (CAC) as a decentralized care pathway transcending all stages: (1) case finding and pre-test counseling, (2) testing and post-test counseling, (3) treatment, and (4) post-treatment care (26, 27). This study aims to evaluate the implementation of the CAC pathway using a context-based implementation framework assessing five outcomes: Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM), as outlined in the published protocol through a mixed methods design (28-30). The primary endpoint of this implementation evaluation was the effectiveness, as indexed by the HCV elimination rate (patients 'cured' divided by patients identified).

Methods

Study Design

This study utilizes a mixed methods design to perform a RE-AIM based evaluation of the implementation of CAC. It firstly includes a multi-center prospective observational cohort study, with data collected from March 2020 until June 2023. Furthermore this study investigates organizational level RE-AIM dimensions. The Research Ethics Committee Arnhem-Nijmegen approved this study (protocol nr. 2019-5939) and exempted this study from the Medical Research Involving Human Subjects Act. More details on design and methods of this study were published previously (30). Trialregistration: NCT05401136

Study Population and setting

All major addiction care facilities in the Netherlands affiliated with the Dutch Addiction Association were asked to participate in this study via email by DV (31). These organizations represent all addiction care providers in the Netherlands that offer comprehensive treatment for individuals with mild to severe substance use disorders, including those with substantial psychiatric or somatic comorbidity. The project focused on outpatient facilities catering to patients at higher risk for bloodborne infections, including outreach services, and methadone programs. Within the participating addiction care facilities HCV-RNA positive PWUD were

identified and asked for written informed consent. Patients were eligible if they were aged 18 years or older and visited participating addiction care centers at least once during the study period. There were no exclusion criteria.

Procedures within the Hepatitis C chain of Addiction Care (CAC) pathway

The CAC pathway was developed in alignment with existing HCV care guidelines [9, 10]. In this model, addiction care physicians (ACPs) and nurses employed by addiction care performed HCV risk assessment, patient education, testing, treatment, and follow-up (suppl. figure 1). The education of local staff was carried out by the research team. The trainings included at least the nurses and physicians. Other staff was welcome to attend, but not part in these training efforts in all sites. Sites were free to implement the protocol as they saw fit for their specific context. Due to variation in availability of resources between sites, no one size fits all approach was used. After educating at least the nurses and physicians on all stages of HCV care, consultation was provided by an outpatient medical specialist in a nearby hospital or the investigator (DvdH) for the duration of the project. After evaluating patient specific factors such as laboratory findings, FIB-4 scores (for liver fibrosis or cirrhosis), hepatitis B or HIV co-infection and potential drug interactions, HCV positive patients received pangenotypic DAA treatment (glecaprevir/pibrentasvir 8-12 weeks or sofosbuvir/velpatasvir 12 weeks). Complex cases, defined as those co-infected with hepatitis B or HIV, severe renal impairment, prior DAA treatment failure, or advanced liver disease (Child-Pugh B or C cirrhosis), were referred to outpatient specialist care. Patients with compensated cirrhosis were co-managed by addiction and hospital care. All patient specific outcomes were retrieved from the electronic patient files. Organization-level outcomes were retrieved from official documentation and correspondence.

Outcomes according to the RE-AIM framework

To comprehensively evaluate the public health impact of the CAC model, outcomes were categorized according to the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, Maintenance). RE-AIM is a widely used implementation science framework designed to assess the real-world applicability of health interventions (28, 29, 32). RE-AIM facilitates the systematic evaluation of both individual-level and organizational-level outcomes and helps to identify barriers and facilitators to successful implementation and sustainability of interventions.

Reach: Reach was assessed as the extent to which the CAC model reached the target population, including the number and proportion of PWUD tested, number of people

testing HCV-antibody (HCV-Ab) and HCV-RNA positive, and the demographic and clinical characteristics of the reached HCV RNA positive population. We obtained anonymized laboratory data from local laboratories affiliated with the participating addiction care centers to assess both HCV testing frequency and corresponding test outcomes.

Effectiveness: The primary outcome of the study was the effectiveness of the entire intervention within the specific local sites participating in this study. We defined this 'elimination rate' as the number of patients that reached sustained virological response (SVR) divided by all identified HCV RNA positive patients included. Other effectiveness outcomes include rate of treatment initiation, treatment completion, and SVR.

Adoption: Adoption was assessed as the number and percentage of organizations that were willing to adopt the CAC model. Adoption data were collected via documented correspondence with the first author and through official documentation and formal decisions to implement the model.

Implementation: We monitored whether all steps of the CAC pathway were implemented and whether any components were omitted. This included verification of adherence to the protocol at each stage of the care pathway through site-level implementation checklists and availability of the data in the electronic patient file. Deviations or inconsistencies such as hospital referrals outside the intended care model or cases of loss to follow-up were documented during consultation.

Maintenance: Follow-up of implementation was not a subject of this study.

Statistical Analysis

Descriptive statistics were utilized to report the study outcomes. Continuous variables were presented as means ($\pm$ standard deviation) or medians (with interquartile range) depending on their distribution, while categorical variables were expressed as percentages. Due to the observational nature of the study and the lack of a control group, no formal sample size calculation was conducted. All analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Reach

We tested a total of 870 patients for HCV, of which 15% (n=134) were antibody positive (Figure 1). HCV-RNA positivity was present in 3.6% of tested patients (n=31), which amounts to 23% of HCV antibody positive patients.. The 31 HCV RNA positive patients were invited to participate in the study. All patients were eligible for inclusion. However, two patients did not provide informed consent, resulting in a total of 29 HCV-RNA positive PWUD included in the study (Table 1).

Participants were mostly male (n=27, 93%), with a mean age of 51 years. Comorbidities were relatively common, with 31% of participants diagnosed with COPD (n=9), 10% with cardiovascular disease (n=3), and single cases of malignancy (3%), HIV (3%), and HBV (3%). A history of intravenous drug use was reported in 76% of patients (n=22). The most frequently reported current substances used were alcohol (n=15, 52%), heroin (n=8, 28%), cannabis (n=7, 24%), and cocaine (n=4, 12.8%). The majority (83%) of patients were receiving opioid agonist therapy with methadone (n=23), one patient used buprenorphine.

Liver fibrosis was assessed with FIB-4. The median FIB-4 score was 1.5 (interquartile range 0.9 to 3.7). Of all participants, 30% (n=7) had a FIB-4 score above 3.25. There were 7 patients with cirrhosis, Child-Pugh score A (n=6), C (n=1). The mean ALT level at diagnosis was 80 U/L.

Effectiveness

In total, 29 HCV RNA positive patients were included. Treatment was initiated in 26 out of 29 (90%) patients. The overall treatment completion rate was 100%, with all 26 patients completing the full course of therapy. SVR was achieved in 25 out 26 (96.1%) patients, as one patient was lost to follow-up before confirmatory HCV-RNA test. The resulting viral elimination rate was 86.2% (25/29). Two participants were lost to follow-up prior to starting treatment and one refused treatment. Three patients were referred to specialized HCV treatment centers because of co-infection with hepatitis B (n=1), HIV (n=1) or decompensated cirrhosis (n=1). Thus, decentralized (on-site) treatment was provided to 23 out 29 (79%) of participants. Decentralized pangenotypic treatment regimens consisted of sofosbuvir/velpatasvir in 54% (n=12) and glecaprevir/pibrentasvir in 46% (n=11). Adverse events were reported in two patients: one experienced fatigue and the other reported pruritus. No serious adverse events (SAEs) were reported during the study.

Table 1. Demographics and characteristics of study participants (n = 29)

	Total n (%)
Total	29
Male	27 (93)
Age at inclusion (y) (SD)	51 (11)
Region of origin	
Netherlands	17 (59)
Europe (non-Dutch)	7 (24)
Asia	3 (10)
Other	2 (7)
Body Mass Index (SD)	22 (4)
Comorbid conditions	
COPD	9 (31)
Cardiovascular disease	3 (10)
Malignancy	1 (3)
HIV	1 (3)
HBV	1 (3)
Receiving opioid agonist treatment	23 (83)
Previous intravenous drug use	22 (76)
Current drug use	
Alcohol	15 (52)
Heroin	8 (28)
Cannabis	7 (24)
Cocaine	4 (13)
Laboratory findings	
FIB-4 median (IQR) ¹	1.5 (0.9;3.7)
FIB-4 >3.25	7 (30)
Child Pugh Score (in patients with FIB-4 >3.25)	6 (86)
A	0 (0)
B	1 (14)
C	
CKD class 1 or 2 (GFR >60) ²	23 (100)
ALT (SD)	79.8 (57)
INR (range) ³	1.0 (1.0;1.1)
Platelets (SD) ⁴	220 (101)

SD: standard deviation, IQR: Interquartile range, CKD: Chronic kidney disease, GFR: Glomerular filtration rate, ALT: Alanine Transaminase, INR: International Normalized Ratio. Number of patients missing finding 1:n=6; 2:n=6; 3 n=10; 4: n=6

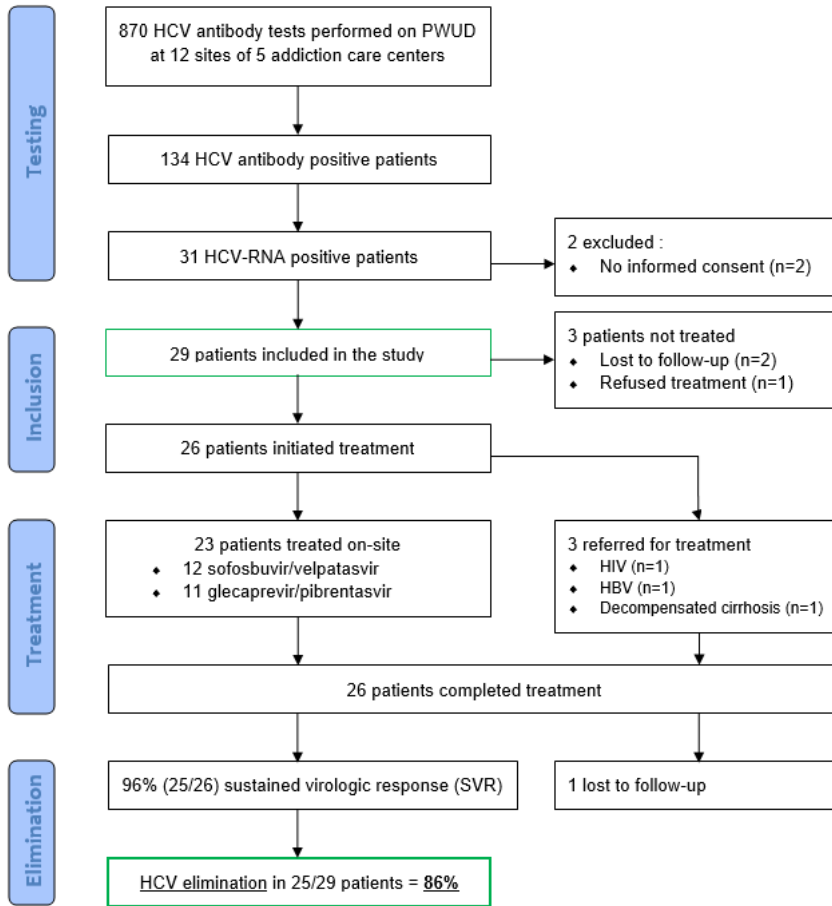


Figure 1. Patient flowchart

Adoption

Out of the eleven addiction care organizations invited to participate in the study, five agreed to adopt the CAC model, representing an adoption rate of 45%. These five organizations accounted for a total of twelve participating sites. These organizations provide comprehensive treatment for patients with mild to severe substance use disorders, including those with significant psychiatric or somatic comorbidity. Their services typically encompass outpatient care, inpatient detoxification and rehabilitation, supervised and supported residential facilities, ambulatory treatment, case-management programs, and prevention in cooperation with municipal public health services. Six large addiction care organizations with comparable service structures did not participate. Within the participating organizations, only a subset of treatment locations was included as study sites.

These sites were selected by the organizations themselves based on willingness and staff and resource availability. The selected sites were predominantly situated in larger cities or major regional centers, rather than smaller towns or rural areas. A table presenting approximate number of patients per organization and the number of site is available (supplementary table 1). The number of patient inclusions per addiction care organization ranged from one to fourteen, with a median of five. These findings reflect moderate adoption at the organizational level.

Implementation

Fidelity to the CAC model was high across all participating sites. No protocol deviations or inconsistencies with the predefined CAC pathway were identified besides one patient missing a week of treatment without clinical consequences. All observed hospital referrals were clinically justified and aligned with the CAC model, as described above. As instructed in the pathway, addiction care remained actively involved in the care of referred patients, providing support and ensuring continuity throughout the specialized HCV treatment trajectory. Only two cases were lost to follow-up prior to treatment initiation, indicating generally robust implementation within the decentralized care setting.

Discussion

This study shows excellent effectiveness of a fully decentralized HCV care pathway in a PWUD population, with an HCV elimination rate of 86% (25 out of 29 identified patients). Of all patients identified, the vast majority initiated treatment (90%), with an SVR of 96% (25 out of 26 treated participants). Adoption of the care pathway among addiction care facilities was moderate, with only five out of eleven invited organizations participating. The implementation process was characterized by strong fidelity to the protocol, with all people initiating treatment also finalizing it and minimal loss to follow-up. Furthermore, the three referrals to outpatient specialist care were clinically justified and appropriately supported by addiction care teams. Application of the RE-AIM framework enabled a thorough understanding of the implementation process, with adoption being the weakest aspect of implementation of the decentralized HCV care pathway.

We performed nearly 900 HCV antibody tests and found a positivity rate of 15% ($n = 134$). This is lower than an earlier nationwide Dutch intervention study from 2009 studying PWID (33). That study was conducted across eleven addiction care centers, which reported 1,130 HCV antibody tests with a positivity rate of 26%

(n = 299). Similarly, the proportion of HCV-RNA positivity amongst HCV antibody-positive individuals was substantially lower in our study (23%) compared to 86% in 2009 (33). The reduced prevalence of chronic HCV in our cohort might indicate successful attempts to eliminate HCV in PWUD in The Netherlands over the past fifteen years, through preventive and treatment measures (e.g. information campaigns, needle exchange- and methadone programs) and low prevalence (<0,1 per 1000) of intravenous drug use (26, 27, 34, 35).

Our findings on treatment initiation and elimination accord with international studies evaluating decentralized HCV care among PWUD (36, 37). For instance, a randomized controlled trial by Fadnes et al. (2020) reported similar rates of treatment initiation (98%) and elimination (83%) (38). Importantly, willingness to initiate treatment in our cohort (90%) and in the study of Fadnes et al. has increased substantially since the peginterferon-era, when willingness to start treatment was 77%, and only 16% were treated (39). Thus, our findings underscore a marked improvement in treatment uptake and elimination outcomes among PWUD in the DAA era, aligning with international evidence and highlighting the acceptability and effectiveness of current HCV care models.

The effectiveness observed within our study on fully decentralized HCV care exceeds that reported in other, less decentralized approaches. Wade et al. (2019), for example, documented lower initiation (75%) and elimination rates (49%) in primary care settings (40). Models characterized by partial decentralization, such as collaboration with outpatient specialty care or temporary specialist clinics embedded within primary care settings, as used by Wade and colleagues, may foster lower levels of patient engagement compared to fully integrated HCV care offered with addiction services. This is in line with recent meta-analysis showing that full decentralization, that combines testing and treatment at the same site, achieved the best linkage-to-care rates (72%), compared to specialist care without decentralization (47%) (37). Shifting HCV management responsibilities directly to dedicated addiction care staff enhances patient involvement and outcomes; this accords with findings from a Dutch cluster-randomized trial by Kruis et al. (2014), in which integrated COPD management in primary care delivered by general practitioners, nurses, and physiotherapists led to improved care coordination and patient activation, without compromising clinical outcomes (41).

Of the eleven organizations invited, five (45%) agreed to participate, indicating a moderate level of adoption. The selected sites were predominantly situated in larger cities or major regional centers, rather than smaller towns or rural areas.

This sampling strategy may have resulted in underrepresentation of more sparsely populated regions, where service availability and patient volumes differ from urban environments. Though data on wider adoption of decentralized HCV care models are limited, our recent qualitative study on barriers and facilitators of implementation identified several barriers for implementation in addiction care (42). Amongst the most often mentioned barriers were the low perceived prevalence of HCV and the opinion that addiction care should not be responsible for somatic treatment. However, our data support the feasibility of HCV care within addiction settings, thereby questioning the validity of excluding somatic health responsibilities from addiction care. The results of our qualitative study also show that both staff and patients supported the decentralized model, while emphasizing the need for sustained resources and coordination to ensure scalability. In addition, international studies also identified lack of resources, reimbursement, lack of peer support programs, limited availability of HCV case managers and the need to refer people for off-site phlebotomy and HCV therapy as barriers (43-45).

Our data demonstrated strong patient fidelity with the CAC pathway. Our findings suggest that the majority of HCV PWUD cases can be managed in addiction care, as all referrals to specialist care were justified due to comorbidity. This finding is supported by current HCV guidelines for simplified HCV treatment (17, 18). Importantly, even in centers with minimal inclusion (i.e. one patient), the protocol was adhered to, and treatment was effective. This indicates that the model can be successfully implemented even in low-volume settings. This includes patients with advanced or comorbid disease such as compensated liver cirrhosis, who were safely and effectively supported within addiction care. Implementation feasibility was influenced by other factors beyond the scope of this study, as they were studied in a qualitative analysis (42). In short, barriers included staff availability, competing clinical priorities, and perceived low HCV prevalence. Professionals generally reported that integrating HCV tasks into daily routines was manageable, although electronic patient systems posed a practical limitation, for instance the absence of automated reminders for screening or SVR testing. Additional facilitators included the central role of addiction-care nurses, alongside perceived support from outpatient specialists. The results of our qualitative study also show that both staff and patients supported the decentralized model, while emphasizing the need for sustained resources and coordination to ensure scalability.

This study's key strength is the prospective multi-center design with inclusion of diverse addiction care settings across various regions in the Netherlands, enhancing the real-world relevance and generalization of the findings. Nonetheless, several

limitations must be acknowledged. The modest number of treated patients ($n = 29$) limits the strength of our conclusions concerning effectiveness. While the broad regional representation mitigates some concerns, sampling bias remains possible due to variability in local HCV prevalence and differences in organizational engagement. This may have led to overrepresentation of certain regions and underestimation of the model's potential reach. Also, as patients who tested negative were not included, there is no data on retesting which restricts the ability to evaluate follow-up testing or to detect reinfections. Finally, the total number of patients at risk at the study sites was not available, which means that a testing rate can't be calculated. Although these limitations may have influenced the depth and generalizability of the outcomes, the consistent fidelity to the protocol and high HCV elimination across settings provide reassurance regarding the robustness and scalability of the model. Finally, long-term sustainability of the CAC model was not assessed in this study and warrants future longitudinal evaluation as described by the RE-AIM framework (32). Longitudinal mixed-methods studies, as recommended by RE-AIM, may be useful to monitor the durability of implementation and clinical outcomes over time (28).

In conclusion, this study demonstrates that the fully decentralized CAC model is not only highly effective in achieving HCV elimination (86%) within addiction care, but also feasible and safe, even for patients with complex comorbidities. The moderate level of adoption (45%) emerged as the main limitation to broader expansion of the program, indicating that future efforts should prioritize strategies to enhance organizational engagement.

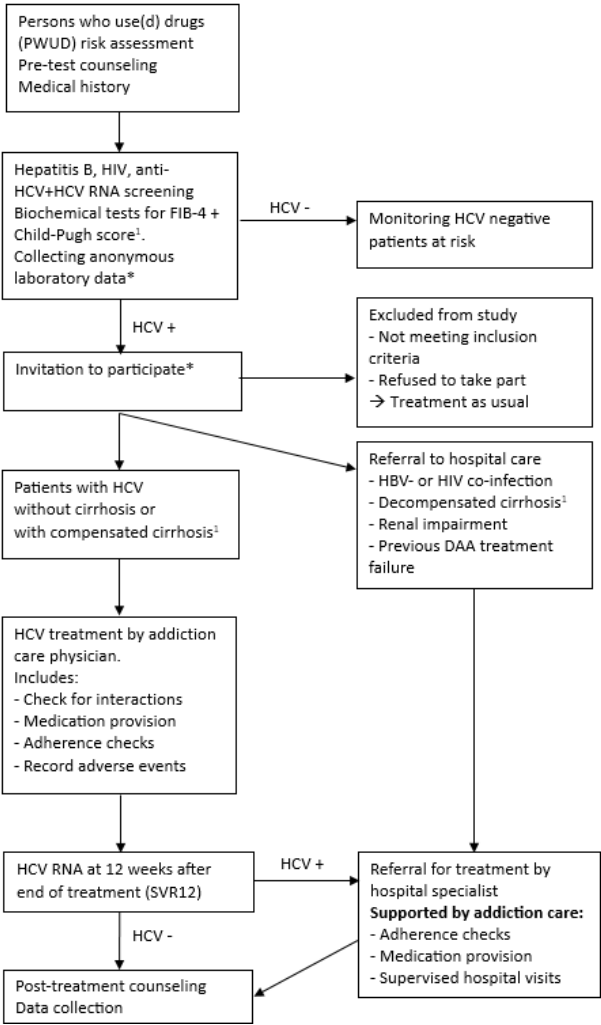
References

1. WHO. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. 2022.
2. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. *The Lancet*. 2019; 394(10207):1451-66.
3. Gamkrelidze I, Pawlotsky JM, Lazarus JV, Feld JJ, Zeuzem S, Bao Y, et al. Progress towards hepatitis C virus elimination in high-income countries: An updated analysis. *Liver Int*. 2021;41(3):456-63.
4. van Dijk M, Brakenhoff SM, Isfordink CJ, Cheng WH, Blokzijl H, Boland G, et al. The Netherlands Is on Track to Meet the World Health Organization Hepatitis C Elimination Targets by 2030. *J Clin Med*. 2021;10(19).
5. Fleurence RL, Alter HJ, Collins FS, Ward JW. Global Elimination of Hepatitis C Virus. *Annu Rev Med*. 2025;76(1):29-41.
6. Maticic M, Cernosa J, Loboda C, Tamse J, Rigoni R, Duffell E, et al. How far are we? Assessing progress in hepatitis C response towards the WHO 2030 elimination goals by the civil society monitoring in 25 European countries, period 2020 to 2023. *Harm Reduct J*. 2024;21(1):203.
7. Kracht PAM, Arends JE, van Erpecum KJ, Urbanus A, Willemse JA, Hoepelman AIM, et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. *Hepatol Med Policy*. 2018;3:12.
8. WHO. Implementing the global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022–2030: report on progress and gaps 2024, second edition. 2024.
9. Koopsen J, van Steenbergen JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. *Epidemiol Infect*. 2019;147:e147.
10. van Dijk M, Drenth JPH, HepNed study g. Loss to follow-up in the hepatitis C care cascade: A substantial problem but opportunity for micro-elimination. *J Viral Hepat*. 2020;27(12):1270-83.
11. Von den Hoff DW, Berden FAC, Atsma F, Schellekens AFA, Drenth JPH. Against All Odds? Addiction History Associated with Better Viral Hepatitis Care: A Dutch Nationwide Claims Data Study. *J Clin Med*. 2022;11(4).
12. Phillips C, Schulkind J, O'Sullivan M, Edelman N, Smith HE, Verma S, et al. Improving access to care for people who inject drugs: Qualitative evaluation of project ITTREAT-An integrated community hepatitis C service. *J Viral Hepat*. 2020;27(2):176-87.
13. Mittal A, Kosinski KC, Stopka TJ. HCV treatment access among Latinxs who inject drugs: qualitative findings from Boston, Massachusetts, 2016. *Harm Reduct J*. 2019;16(1):44.
14. Assoumou SA, Sian CR, Gebel CM, Linas BP, Samet JH, Bernstein JA. Patients at a drug detoxification center share perspectives on how to increase hepatitis C treatment uptake: A qualitative study. *Drug Alcohol Depend*. 2021;220:108526.
15. Tsui JI, Barry MP, Austin EJ, Sweek EW, Tung E, Hansen RN, et al. 'Treat my whole person, not just my condition': qualitative explorations of hepatitis C care delivery preferences among people who inject drugs. *Addict Sci Clin Pract*. 2021;16(1):52.
16. Hopwood M, Treloar C. Under the watchful eye of 'a benevolent dictator' - general practitioner and patient experiences of hepatitis C treatment initiation and shared-care in general practice. *Aust Fam Physician*. 2013;42(12):900-3.
17. EASL eee, Clinical Practice Guidelines Panel C, representative EGB, Panel m. EASL recommendations on treatment of hepatitis C: Final update of the series(). *J Hepatol*. 2020;73(5):1170-218.

18. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology*. 2020;71(2):686-721.
19. Ghosh A, Mahintamani T, Premkumar M, Basu D, Singh V, Duseja A, et al. Multidisciplinary and Integrated Treatment for Substance Use Disorders and Hepatitis C in an Addiction Treatment Service in India. *Indian J Psychol Med*. 2023;45(2):193-7.
20. Yu ML, Tai CM, Mo LR, Kuo HT, Huang CF, Tseng KC, et al. An algorithm for simplified hepatitis C virus treatment with non-specialist care based on nation-wide data from Taiwan. *Hepatol Int*. 2024;18(2):461-75.
21. Hassan MRA, Chan HK, Nordin M, Yahya R, Sulaiman WRW, Merican SAA, et al. Assessing feasibility of a modified same-day test-and-treat model for hepatitis C among rural people who inject drugs. *Harm Reduct J*. 2023;20(1):48.
22. Dhiman RK, Grover GS, Premkumar M, Taneja S, Duseja A, Arora S, et al. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. *J Hepatol*. 2019;71(6):1076-85.
23. Busschots D, Bielen R, Koc OM, Heyens L, Dercon E, Verrando R, et al. On-site testing and case management to improve hepatitis C care in drug users: a prospective, longitudinal, multicenter study in the DAA era. *BMC Public Health*. 2021;21(1):1574.
24. Bregenzer A, Bruggmann P, Castro E, Moriggia A, Rothen M, Thurnheer MC, et al. Hepatitis C virus elimination in Swiss opioid agonist therapy programmes - the SAMMSU cohort. *Swiss Med Wkly*. 2021;151:w20460.
25. Schatz E. IDPC Briefing Paper The Dutch treatment and social support system for drug users. International Drug Policy Consortium. 2011.
26. Kracht PAM, de Gee EA, van der Poel A, Verhagen M, Hoepelman AIM, Croes EA, et al. Introducing hepatitis C virus healthcare pathways in addiction care in the Netherlands with a Breakthrough project: a mixed method study. *Harm Reduct J*. 2019;16(1):45.
27. Trimbos. Blueprint – Hepatitis C care pathway for clients in addiction care. Utrecht; 2017.
28. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. *Front Public Health*. 2019;7:64.
29. Sweet SN, Ginis KA, Estabrooks PA, Latimer-Cheung AE. Operationalizing the RE-AIM framework to evaluate the impact of multi-sector partnerships. *Implement Sci*. 2014;9:74.
30. Von den Hoff DW, Berden FAC, Drenth JPH, Schellekens AFA, HepNed N. Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care. Study protocol for the Hepatitis C: chain of addiction care (CAC) project. *Addict Sci Clin Pract*. 2022;17(1):67.
31. VKN. 2025 [Available from: <https://verslavingskudenederland.nl/we-are-daa/>].
32. Holtrop JS, Estabrooks PA, Gaglio B, Harden SM, Kessler RS, King DK, et al. Understanding and applying the RE-AIM framework: Clarifications and resources. *J Clin Transl Sci*. 2021;5(1):e126.
33. Helsper CW, Janssen MP, van Essen GA, Croes EA, van der Veen C, de Wit AG, et al. Effectiveness and cost-effectiveness of nationwide campaigns for awareness and case finding of hepatitis C targeted at people who inject drugs and the general population in the Netherlands. *Int J Drug Policy*. 2017;47:117-25.

34. Van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M, Amsterdam C. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007;102(9):1454-62.
35. Nationale Drug Monitor. Opiaten 5.6 Hulpvraag en incidenten - Nationale Drug Monitor: Trimbos-instituut, Utrecht & WODC, Den Haag; 2022 [Available from: <https://www.nationaledrugmonitor.nl/opiaten-hulpvraag-en-incidenten/>].
36. Cunningham EB, Wheeler A, Hajarizadeh B, French CE, Roche R, Marshall AD, et al. Interventions to enhance testing, linkage to care, and treatment initiation for hepatitis C virus infection: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7(5):426-45.
37. Oru E, Trickey A, Shirali R, Kanters S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health*. 2021;9(4):e431-e45.
38. Fadnes LT, Aas CF, Vold JH, Leiva RA, Ohldieck C, Chalabianloo F, et al. Integrated treatment of hepatitis C virus infection among people who inject drugs: A multicenter randomized controlled trial (INTRO-HCV). *PLoS Med*. 2021;18(6):e1003653.
39. Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug Alcohol Depend*. 2008;93(1-2):141-7.
40. Wade AJ, Doyle JS, Gane E, Stedman C, Draper B, Iser D, et al. Outcomes of Treatment for Hepatitis C in Primary Care, Compared to Hospital-based Care: A Randomized, Controlled Trial in People Who Inject Drugs. *Clin Infect Dis*. 2020;70(9):1900-6.
41. Kruis AL, Boland MR, Assendelft WJ, Gussekloo J, Tsiachristas A, Stijnen T, et al. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. *BMJ*. 2014;349:g5392.
42. Von den Hoff DW, Ellerbroek H, Drenth JPH, Berden FAC, Schellekens AFA. Facilitators and barriers for implementation of a decentralized hepatitis C care chain for people who use drugs in Dutch addiction care. *Drug Alcohol Depend*. 2025;274:112759.
43. Litwin AH, Drolet M, Nwankwo C, Torrens M, Kastelic A, Walcher S, et al. Perceived barriers related to testing, management and treatment of HCV infection among physicians prescribing opioid agonist therapy: The C-SCOPE Study. *J Viral Hepat*. 2019;26(9):1094-104.
44. Bredenberg E, Callister C, Dafoe A, Holliman BD, Rowan SE, Calcaterra SL. Subspecialty physicians' perspectives on barriers and facilitators of hepatitis C treatment: a qualitative study. *Harm Reduct J*. 2024;21(1):140.
45. Marshall AD, Grebely J, Dore GJ, Treloar C. Barriers and facilitators to engaging in hepatitis C management and DAA therapy among general practitioners and drug and alcohol specialists- The practitioner experience. *Drug Alcohol Depend*. 2020;206:107705.

Supplementary files



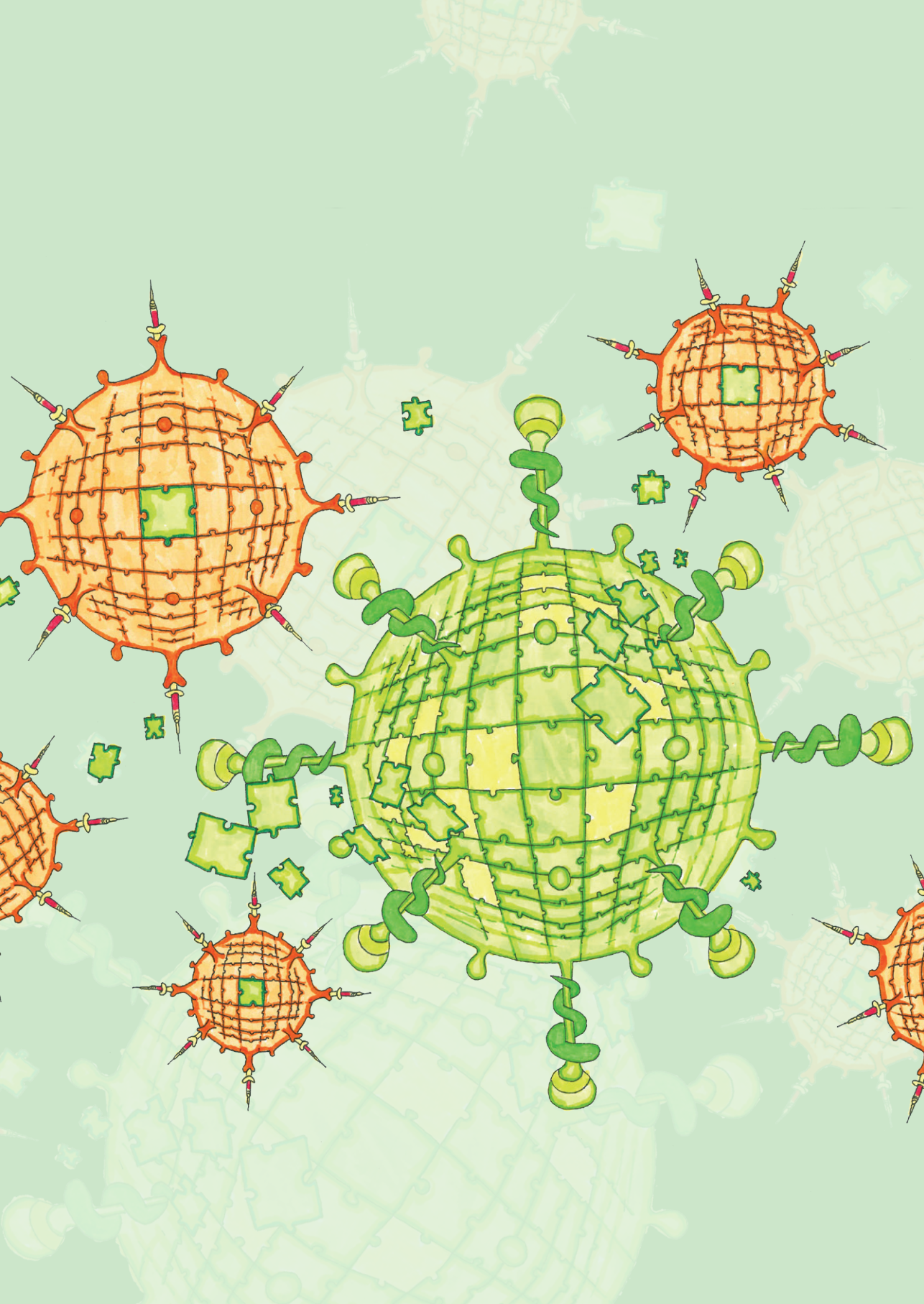
Suppl.figure 1: Adjusted CAC and study flowchart

*modified compared to original protocol

Suppl. Table 1. Number of sites and patients per participating addiction care organization, as supplied by the organization. (index year varied between 2021-2024)

Organization	Irishzorg	Tactus	Jellinek	Brijder	VNN*
Sites	60	46	14	1	36
Number of patients	~9600	8920	6229	~6500	9552

*Verslavingszorg Noord Nederland



Chapter 6

Facilitators and barriers for implementation of a decentralized hepatitis C care chain for people who use drugs in Dutch addiction care

Daan W. Von den Hoff

Hannah Ellerbroek

Joost P.H. Drenth

Floor A.C. Berden

Arnt F.A. Schellekens

Abstract

Background: People who use drugs (PWUD) are an important target population for HCV elimination goals of the World Health Organization (WHO). Case-finding and treatment of these patients is challenging due to population specific barriers like stigma and care avoidance. Low threshold HCV screening and treatment within addiction care may facilitate viral elimination. This study aims to identify facilitators and barriers to implement HCV care within addiction care.

Methods: In this qualitative study we conducted semi-structured interviews with fifteen physicians, nurses and policy makers of addiction care centers with varying degrees of HCV care implementation as well as a gastroenterologist and an infectiologist. The barriers and facilitators resulting from the interviews were coded, themed, and categorized using thematic analyses.

Results: Major barriers to implementation of HCV care within addiction care included slow decision-making processes in large addiction centers, limited financial and personnel resources, comorbidity and missed appointments, and low HCV prevalence hindering expertise development. Crucial facilitators were the role of nurse specialists, patient familiarity and trust in addiction care staff, and increased treatment adherence. Despite low prevalence, managing uncomplicated HCV cases was deemed feasible with minimal expertise.

Conclusions: Implementation of HCV care within addiction care was generally enthusiastically received by participants. Identified organizational, staff, patient, and HCV treatment-related barriers and facilitators can aid in the implementation of integrated HCV-addiction care, thus contributing to WHO HCV elimination goals.

Introduction

Hepatitis C virus (HCV) infection is a serious public health threat, affecting around 71 million people globally (1). In the Netherlands, people who injected drugs are the population with the highest estimated prevalence of HCV infection at 59% (range 35%-84%) (2). Though patients infected with HCV generally remain asymptomatic, long-term HCV infection can lead to liver cirrhosis and hepatocellular carcinoma. It is therefore a leading cause of liver-related morbidity and mortality, especially among people who use(d) drugs (PWUD) (3).

Effective treatment for HCV is available through direct-acting antiviral (DAA) therapy, with cure rates up to 99% (4). HCV care is generally provided by infectiologists or gastroenterologists in outpatient specialty care. Literature suggests that for PWUD, accessing outpatient care can be challenging, for instance due to lack of trust in providers, financial constraints, and limited capacity to travel (5). PWUD can furthermore face stigma and discrimination, which could lead to suboptimal care or deter them from seeking care (6).

Decentralized HCV care, consisting of HCV screening and DAA prescription in addiction care facilities, can improve HCV treatment access for PWUD (7). This concept is facilitated by simplified HCV testing and liver disease assessment, for instance the FIB-4 score (4, 8). In some countries, addiction care centers have successfully integrated HCV care into their services, and these initiatives show promising results in terms of linkage to care and HCV elimination (9).

Only a few studies explored barriers and facilitators of this model and the studies that have been performed focus mainly on patient perspectives. These studies highlight barriers to HCV care, such as poor vein health, fear of having to quit substance use and stigma (6, 10, 11). One study performed in general practitioners shows that non-specialist HCV care providers may not possess adequate knowledge on HCV management (12). Furthermore, these facilities may not have enough staff, laboratory services or funding to provide HCV testing and treatment and they face competing priorities in care provision (5, 13-15).

Insight in facilitators and barriers for implementation of HCV care within addiction care, from the perspective of addiction care providers, outpatient specialists and policy makers, is essential for wide scale implementation of decentralized HCV care, and subsequent HCV eradication among PWUD. We therefore performed

a qualitative study among these professionals, to explore relevant themes to aid implementation of decentralized HCV care within Dutch addiction care.

Methods

Study design and participant recruitment

We conducted a qualitative study with face-to-face semi-structured interviews. We recruited addiction nurses, addiction care physicians (ACP) and addiction care policy makers across the Netherlands. Furthermore, although not originally part of our target group, one infectiologist and one gastroenterologist were included following suggestions from early participants, who indicated that their perspectives would contribute to a more comprehensive understanding of the context. Participants were approached by e-mail (by DV) through two expertise networks; the Dutch Addiction Association and the Dutch national viral hepatitis network (16, 17). To collect diverse perspectives on the subject we used purposive sampling to achieve a variety in participant's age, gender and experience, as well as varying degrees of implementation of decentralized HVC care in their working context. Participants were recruited until data saturation was reached.

No financial compensation for participation was provided. All participants provided written informed consent. The project was exempted from ethical approval by the regional ethical committee (CMO Arnhem Nijmegen), according to Dutch law on medical research (protocol nr. 2022-13584). The consolidated criteria for reporting qualitative studies (COREQ) checklist (18), was used to systematically report data (supplement 1).

Setting

In the Netherlands, addiction care is provided by regional addiction care centers across the country. As a result, addiction care is widely available, covered by health insurance and accessible to everyone through referral from general practitioners. Addiction care centers provide prevention, treatment and harm reduction services (e.g., needle exchange), provided by ACP, nurses, psychologists and supporting staff. Addiction care plays a pivotal role in supporting PWUD and promoting public health (19). The majority of Dutch people with opioid use disorders are in (agonist) treatment, and injecting drug use rates are low (20). Several centers participated in a pilot project integrating HCV management into addiction care, where ACP and nurses performed risk assessments, patient education, testing, treatment, and

follow-up of HCV in the addiction care setting; this pilot was conducted in five large addiction care organizations between March 2020 and June 2023(21).

Data collection

All interviews were conducted by one author, DV (medical doctor experienced in both addiction and outpatient care, HCV researcher), who received training and observation with feedback by a colleague experienced in conducting semi-structured interviews (LD, see acknowledgements). An interview guide with a topic list (supplement 2) was composed by authors DV, FB (gastroenterologist) and AS (psychiatrist specialized in addiction care) based on literature review. The interview guide contained open-ended questions designed to elicit detailed responses. The interviewer asked follow-up questions to expand and clarify viewpoints. Participants were encouraged to suggest additional relevant topics.

The audio was recorded with the participant's consent and removed within 24 hours after verbatim transcription by DV. Field notes were taken during the interviews on emerging themes. At the end of the interview, participants were invited to send feedback or additional information to the interviewer by e-mail.

Data analysis

Braun and Clarke's approach to thematic analysis was used to identify relevant themes (22). This analysis involved a six-phase process: familiarization with the transcripts, coding, searching for themes, reviewing themes, defining and naming themes and writing the manuscript. Each transcript was coded by two researchers (DV and HE (researcher in addiction care)) independently, using ATLAS.ti v22. The coding process was data driven, following an inductive method. In this stage, codes were also characterized as barriers or facilitators. In addition, relevant quotations of participants were selected. The codes of each transcript were compared between the two researchers, and irregularities were resolved in a consensus meeting.

Themes were derived from the data (Grounded Theory) in four thematization sessions where DV, HE, FB and AS were present. During these sessions, which took place every three to five interviews, the topic list was revised based on participant feedback. Previous participants were not re-contacted to address additional topics. These sessions were also used to assess thematic data saturation based on established principles (18). When the study team agreed that consecutive interviews rendered no new insights, data saturation was reached. The interviews, codes and themes were all gathered in Dutch, the themes and quotations were then translated to English by DV and discussed with the co-authors until consensus.

Findings

Participants

In this study, fifteen participants were interviewed. Seven were male, age ranged between 31 and 62 years (Table 1). Majority of the participants (13/15) were employed by addiction care centers, nine at centers participating in a Dutch HCV decentralization effort (21); five participants were ACP, four (specialized) nurses, four board members and/or policy makers. Additionally, we interviewed an infectiologist and a gastroenterologist. The duration of the interview ranged from 28 to 62 minutes.

Table 1. Participant characteristics.

Participant	Age (years)	Gender	Profession	Experience in the field (years)	Participated in decentralization project
1	48	Male	ACP	18	Yes
2	64	Male	ACP	15	Yes
3	35	Male	ACP	7	Yes
4	63	Female	ACP	15	No
5	46	Female	ACP	6	Yes
6	62	Female	Nurse practitioner	20	No
7	43	Female	Nurse practitioner	6	Yes
8	64	Male	Nurse	13	Yes
9	50	Female	Nurse	14	No
10	60	Female	Infectious Disease consultant	21	Yes
11	44	Female	Research coordinator	15	No
12	55	Male	Head of Research	8	Yes
13	39	Female	Care Manager	4	Yes
14	40	Male	Gastroenterologist and Hepatologist	5	N.A.*
15	63	Male	Infectiologist	31	N.A.*

*Hepatitis C: Chain of addiction care’ is a Dutch HCV decentralization project in addiction care (21). Participant 14 and 15 were employed by hospitals and participation is therefore not applicable.

Barriers and facilitators for implementation of HCV decentralization

We identified four themes relevant to implementation of decentralized HCV care in addiction care; organizational factors, staff factors, factors related to HCV and patient factors. Each theme contained several facilitators and barriers (Table 2). The participant numbers at the end of the quotations correspond to the participants in Table 1.

Table 2. Barriers and facilitators for implementation of decentralized HCV care in Dutch addiction care.

	Barriers (-)	Facilitators (+)
Organizational factors	Slow transition of policy into clinical practice. Lack of personnel dedicated to implementation (HCV project leaders). No extra funds or time in addiction care for HCV treatment.	Local HCV care is less time consuming than accompanying patient to outpatient specialist care. Establishing a network for HCV treatment also benefits management of other (infectious) diseases. HCV medication is insured
	Both Barrier and Facilitator (-/+) <i>Participants described variation in enthusiasm from- and quality of collaboration with the local hospitals.</i>	
Staff factors	Loss of expertise due to frequent personnel turnover. Part of staff has the opinion that addiction care should not be responsible for treating somatic disease. Hesitancy to act in unfamiliar situations	Addiction care nurses are trained in motivational interviewing. Sense of improvement of the quality of care. Addiction care staff can identify when patients are ready for HCV treatment. No stigma towards HCV in addiction care. Patients trust addiction care personnel.
Patient factors	Missed appointments due to discrepancy in patient needs and care adaptability. Psychological comorbidity is common in the population. Low-threshold treatment may lead to an underestimation of disease severity in patients. Risk for unfinished treatment due to abovementioned barriers.	Patients may be more compliant to addiction care compared to outpatient specialist care
Hepatitis C testing and treatment	Low prevalence of HCV makes it difficult to gain expertise. Technical restrictions (no ultrasound) limit follow-up for cirrhosis. Difficult to add new functionalities (HCV-related) in outdated electronic medical report system. No guideline yet for HCV testing and treatment in addiction care.	Treatment required minimal knowledge and experience in most cases. Elimination (even without follow-up) has health benefits for patients. HCV treatment can be a catalyst for other positive changes in a patient's life (addiction treatment, lifestyle changes).

Organizational Factors: Barriers

Slow processes: Many participants described a large variation in the organizational structure of addiction care centers. As a result, different centers (e.g. large regional multicenter institutions versus small local facilities) required different project management strategies, making a uniform approach to implementation more difficult. Most participants in large centers highlighted a slow decision-making process as a barrier for new project implementation, due to multiple organizational layers and a hierarchical form of decision-making leading to bureaucratic hurdles.

*"The organization has grown so tremendously that I honestly have no clue anymore who is where and in charge of what, and that's a shame."
(participant 10)*

Resources and funds: Although HCV medication is covered by general health insurance, many participants in addiction care mentioned limited funds for HCV management as no reimbursement for time invested or appointment of dedicated HCV project leaders is available. One participant questioned the professionalism of institutions that would disregard HCV due to costs:

"Some claim to be addiction treatment facilities, but then mainly focus on costs and when it comes to hepatitis C, they tell patients to go somewhere else." (participant 3)

Organizational Factors: Facilitators

Saving time: Several participants mentioned that integrating HCV care within addiction care is less time consuming than facilitating referral and treatment in the outpatient specialist care. Nurses would often accompany patients to outpatient care appointments, which is not necessary in decentralized HCV treatment.

"It saves you the trouble of having to refer someone or coordinate with a general practitioner. Instead, you can get started right away, which I think saves time." (participant 3)

Establishing networks: A few participants who had noticed hesitancy with colleagues due to the low HCV prevalence, mentioned that an established network of professionals collaborating in HCV management could also be used to prevent and treat other infectious diseases.

"I don't think that [HCV decentralization] will yield dozens of patients, but it's generally good to have that contact for other forms of viral hepatitis and infectious diseases." (participant 15)

Organizational Factors: Both barrier and facilitator

(Absence of) care chain agreements: The need for clear agreements by defining hospitals' and addiction cares roles in managing HCV among PWUD was identified as an important facilitator when implemented. Key agreements include referral criteria, availability of low threshold case-based support and staff education. Without care chain agreements, addiction staff would feel insecure managing HCV.

"It's nice to have [an expert] to fall back on, so that when there are questions, we can rely on a hospital that knows we are doing this." (participant 5)

(Absence of) enthusiasm: All participants were enthusiastic about HCV management in addiction care and perceived the same sentiment in most colleagues. They believed this enthusiasm facilitates implementation. On the contrary, many also pointed out that enthusiasm is also needed from the local hospital for support, which was often the case. However, when no support was perceived from the hospital, this was a crucial barrier.

"Yes, to me [HCV decentralization] seems like an excellent idea and I am a huge supporter of it. Absolutely, especially with the development of a transmural care pathway, right?" (participant 6)

Staff Factors: Barriers

Personnel turnover: Some participants described a high turnover rate of addiction care staff, which resulted in a loss of expertise in HCV management and need for frequent staff education. One participant mentioned that the low HCV prevalence enhances this problem, due to lack of routine-development.

"They once provided [HCV] training to all of our doctors, and now half of those doctors have already left." (participant 6)

Responsibility: Some participants mentioned that other addiction care staff sometimes feel that they should not be responsible for treating somatic diseases such as HCV, as general healthcare should provide this care. One participant also had this opinion herself.

"I think in the longer term you have to make different choices as addiction care institutions. [...] However [in the short term] we are responsible for our addiction treatment, not for healthcare that can be performed elsewhere." (participant 4)

Hesitance to act: One participant noted that addiction care staff may hesitate to manage HCV due to unfamiliarity, uncertainty and perceived misalignment with their usual duties. He linked this phenomenon to a lack of overview or vision on integrative care models.

"There may be some hesitation to take action in people. Like "that [HCV care] doesn't belong here" or "that doesn't fit here". I think these are signs of a lack of overview and possibly also a lack of clear vision." (participant 12)

Staff Factors: Facilitators

Nurse expertise: All study participants identified specific expertise of addiction care staff, particularly nurses, as key facilitators for implementing decentralized HCV care. Addiction care nurses were described to have a closer relationship with the patients than outpatient specialist care staff and to have a holistic perspective on addiction. They are also trained in motivational interviewing, which helps them to motivate patients. It was also mentioned that specialized nurses are suited to perform standardized treatment of HCV in addiction care, including medication prescription and maintenance.

"Inside every nurse there are feelings like: [this patient] is not here just to be treated for addiction [...] We should look at addiction care from a holistic perspective and support physical health too." (participant 6)

Increased quality of care: Some participants reported a sense of accomplishment by offering HCV care in the addiction setting. They described perceiving an increased quality of care by being able to improve patient's physical health, as well as managing addiction.

"It's rewarding to do something that is effective and feasible, yes, I think that's a very valuable addition and expansion to the profession." (participant 3)

Less stigmatizing attitudes: Most participants in our study noted stigma that accompanies addiction. While many agreed that staff in addiction care settings

may be less stigmatizing than staff in general healthcare settings, it was noted that feelings of shame around having an infectious disease may still be present in patients.

"[Our patients] often feel unheard in the hospital and like there is stigma about whether someone has a history of addiction or currently has an addiction. [...] They feel like they are not seen as a person, but as an addict and they notice this very keenly." (participant 7)

Trust: Almost all participants mentioned that patients are familiar with addiction care personnel and trust them and may therefore be more willing to initiate HCV treatment, compared to going to outpatient specialist care.

"They're aware I've been dispensing methadone for ages, so that's how I try to persuade them, using the trust and the therapeutic relationship you have to motivate them." (participant 9)

Patient Factors: Barriers

Missed appointments: Many participants reported that missed appointments complicate HCV treatment in outpatient medical specialist care. Patients can have difficulties scheduling appointments and furthermore, the complex Dutch health system at times fails to adapt to the patients' needs. Though addiction care might better adapt to these patients' needs, this may still interfere with decentralized HCV care.

"[There are] many competing social and societal issues that require a lot of attention of people [in addiction care] and that causes instability." (participant nr. 7)

Comorbidity: Many addiction care practitioners reported a high prevalence of co-occurring psychiatric disorders, including personality disorders and intellectual disability among their patient population. This may complicate HCV treatment, due to their impact on cognition, behavior and emotional well-being.

"You are working with homeless people who use drugs who almost always have a second or even third psychiatric disorder." (participant nr.7)

Underestimation of HCV severity: One participant expressed the concern that some patients may underestimate the severity of HCV infection, when treatment is offered in addiction care.

"I notice that patients often take somatic care more seriously than our [addiction] services, perhaps precisely because we're so accessible. (Participant nr.4)

Risk for unfinished treatment: Several participants pointed out abovementioned barriers can lead to patients not completing HCV treatment.

"We'll be working with a group where commitment isn't always consistent. [...] So we'll be starting interventions without knowing for sure whether patients will complete them." (participant nr.7)

Patient Factors: Facilitators

Patient compliance with addiction care: All participants predicted that the chance of successful HCV treatment is higher in addiction care compared to outpatient specialist care, as the threshold to participate in HCV care is lower in addiction care. Furthermore, PWUD seem engaged in their addiction treatment, working towards recovery

"They're people who often avoid healthcare and only come because they need their methadone and don't want too much fuss. [...] I think the threshold for participating in [HCV] treatment will be lower here." (participant nr. 9)

Hepatitis C testing and treatment: Barriers

Low HCV prevalence: Many participants highlighted that the low prevalence of HCV among the patient population could make it difficult for staff to maintain and increase their expertise on the clinical management of HCV; as expressed by one participant:

"You just need to see a lot of cases to become sharp in it [...] but in [HCV's] case, I think the number of positive cases is limited." (participant 12)

Technical restrictions: The infectiologist and gastroenterologist as well addiction care specialists reported technical limitations as a barrier to optimal HCV care. For instance, the absence of advanced diagnostic tools like ultrasound and elastography in addiction care centers limits the ability to diagnose and follow up on cirrhosis.

"Ideally, you'd perform an ultrasound or a FibroScan, not necessarily for everyone, but those resources aren't available there." (participant 14)

Outdated electronic reporting systems: Some participants identified outdated electronic medical record systems in addiction care as a significant challenge. Integrating new HCV-related functionalities were described as difficult, as well as the absence of reminders in the system for regular health screenings.

"It would help if you'd get a prompt saying something like, 'It's time for hepatitis C monitoring,' [...] I feel that the current system doesn't really support us proactively in that way." (participant 12)

Support system: Many participants mentioned the wish for a clear concise guideline for managing HCV in addiction care. They highlighted the need for ongoing education for staff on how to manage HCV, with suggestions for more comprehensive training and protocols.

"Knowledge gained, quickly fades away in the daily routine. So, if [HCV care] becomes common practice here, there really needs to be more guidance provided [for addiction care staff]." (participant 10)

6

Hepatitis C testing and treatment: Facilitators

Minimal knowledge and experience required: All participants who treated HCV patients reported that minimal knowledge and experience was needed to manage HCV cases without co-infections, cirrhosis or complex drug-drug interactions and that a broad, protocolized implementation of HCV treatment was considered feasible and promising.

"Yes, [decentralized HCV treatment] was very convenient and very easy in that sense. Of course, organizationally it's a bit challenging, as they're still expensive medications." (participant 3)

Treatment adherence: Most participants reported the possibility in addiction care to combine appointments for addiction treatment with HCV management, increasing adherence to HCV treatment. For example, those treated with methadone can pick up their HCV medication when they pick up methadone.

"It could improve adherence to taking the medication if they receive it at the same time as methadone, because they need that anyway and can pick it up immediately." (participant 9)

Health improvement: A gastroenterologist mentioned that the health benefits from HCV elimination in addiction care is significant, even without extensive follow-up that would normally be provided with outpatient specialist care. Both HCV specialists agreed that addiction care treatment reaches more PWUD than outpatient specialist treatment and is preferable to no treatment at all.

"You treat [HCV] to prevent complications [...] you can say pragmatically: let's just treat. Then you prevent progression and possibly further spread. That would be an argument for just doing it." (participant 14)

Positive changes after treatment: Some participants noted that HCV treatment, besides curing HCV, can serve as a catalyst for other positive changes in patients' lives, such as improved engagement in addiction treatment and lifestyle modifications.

"Treatments that we normally can't get off the ground suddenly work [...] Some [patients] are off drugs and alcohol. It's not just about treating hepatitis; it's about transforming lives." (participant 3)

Discussion

This qualitative study explored barriers and facilitators of decentralized HCV care within Dutch addiction care using semi-structured interviews. In general, the implementation of decentralized HCV care in addiction care was met with enthusiasm. Our study creates a comprehensive overview of organizational, staff-related, treatment-related and patient-related barriers and facilitators.

Organizational challenges, such as slow decision-making processes in mental healthcare facilities have been described in the Dutch system before (23), and financial and staffing issues have also been described in Australia (5, 15) and the USA (24). These issues can significantly weigh down the quality and sustainability of a decentralization effort. Our data suggest that health insurance policies to fund dedicated staff and imbursement of HCV care in addiction care are crucial for implementation. Setting up infectious disease collaboration networks is important as well.

A major facilitator at the staff level was availability of (specialized) nurses in integrated HCV-addiction care. Their strong relationship with PWUD facilitates HCV care within addiction care (25). In accordance with literature, our data suggest that their non-stigmatizing attitudes and communication skills like motivational

interviewing can contribute as well (6, 26). Importantly, regular HCV training is seen as prerequisite to improve and maintain HCV-related expertise despite low exposure to cases. Staff barriers such as high turn-over, hesitancy to act and competing responsibilities may be mitigated by clear guidelines for managing HCV there. Altogether these data argue for nurse-led HCV management in addiction care.

While patient-related factors, including comorbidity and missed appointments were identified, participants agreed that these barriers are preferably managed in addiction care. Interestingly, patient barriers like fear of having to quit alcohol/drugs and poor venous access were not mentioned, though these have been extensively described in literature (6, 10). This might be due to previous widespread information campaigns (27, 28) and the current low prevalence of injecting drug use in the Netherlands (2).

The main treatment-related barrier was the experienced low prevalence of HCV and hence, the limited opportunity to gain expertise with clinical management of HCV. Managing uncomplicated cases (without co-infections, cirrhosis or drug-drug interactions) was perceived as undemanding, in line with data from the USA (24). Literature even describes minimal monitoring approaches as viable, though this has not been studied in a decentralized care setting specifically targeting PWUD (29). Support from local HCV specialists remains crucial to manage more complicated cases including patients with liver cirrhosis (5, 14, 30).

While the study offers valuable insights, potential limitations include sampling bias, as participants are drawn from specific centers, of which some were already acquainted with the decentralization project. This may have resulted in socially desirable responses. To minimize this issue, we actively approached centers that did not participate in HCV projects. Furthermore, we did not include the patient perspective, as patients' viewpoints have been studied extensively before (13, 31, 32). This study provides novel insights from a variety of stakeholders who, with different roles and perspectives, managed to find common ground on the subject. Another strength of this study is the interdisciplinary background of the research team, as it includes specialists in hepatology and addiction. This may have contributed to an overall nuanced understanding of the dynamics around the subject in the Dutch context.

A remaining knowledge gap is the understanding of long-term sustainability and maintenance of decentralized HCV care models. While our study provides insights into the initial implementation phase, future research should focus on

long-term outcomes, including patient retention, health outcomes, and the maintenance of staff expertise over time. This is essential for optimizing the impact of decentralization on HCV elimination.

In conclusion, decentralization of HCV care to addiction care seems highly viable especially with dedicated HCV funding, preferably for (specialized) nurses. Other factors like guidelines need to be in place and collaboration in the care chain should be optimized. While challenges remain, addiction care can become a key-player in HCV management. Insights from this study can provide a clear path to successful implementation of decentralized HCV care within addiction care both in the Netherlands and abroad (33).

References

1. WHO. Report WHO Global health sector strategy on viral hepatitis. Geneva, 2017.
2. Koopsen J, van Steenberghe JE, Richardus JH, Prins M, Op de Coul ELM, Croes EA, et al. Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population. *Epidemiol Infect.* 2019;147:e147.
3. Spearman CW, Dusheiko GM, Hellard M, Sonderup M. Hepatitis C. *The Lancet.* 2019;394(10207):1451-66.
4. EASL Clinical Practice Guidelines Panel C, representative EGB, Panel m. EASL recommendations on treatment of hepatitis C: Final update of the series(). *J Hepatol.* 2020;73(5):1170-218.
5. Marshall AD, Grebely J, Dore GJ, Treloar C. Barriers and facilitators to engaging in hepatitis C management and DAA therapy among general practitioners and drug and alcohol specialists-The practitioner experience. *Drug Alcohol Depend.* 2020;206:107705.
6. Madden A, Hopwood M, Neale J, Treloar C. Beyond interferon side effects: What residual barriers exist to DAA hepatitis C treatment for people who inject drugs? *PLoS One.* 2018;13(11):e0207226.
7. Von den Hoff DW, Berden FAC, Schellekens AFA. If the mountain won't come to Mohammed, then Mohammed must go to the mountain: Decentralisation of hepatitis C care for people who use drugs. *United European Gastroenterol J.* 2021.
8. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology.* 2020;71(2):686-721.
9. Oru E, Trickey A, Shirali R, Kanter S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health.* 2021;9(4):e431-e45.
10. Tsui JI, Barry MP, Austin EJ, Sweek EW, Tung E, Hansen RN, et al. 'Treat my whole person, not just my condition': qualitative explorations of hepatitis C care delivery preferences among people who inject drugs. *Addict Sci Clin Pract.* 2021;16(1):52.
11. Mittal A, Kosinski KC, Stopka TJ. HCV treatment access among Latinxs who inject drugs: qualitative findings from Boston, Massachusetts, 2016. *Harm Reduct J.* 2019;16(1):44.
12. Hopwood M, Treloar C. Under the watchful eye of 'a benevolent dictator' - general practitioner and patient experiences of hepatitis C treatment initiation and shared-care in general practice. *Aust Fam Physician.* 2013;42(12):900-3.
13. Kracht PAM, Arends JE, Hoepelman AIM, Vervoort S. The balancing perspective of hard-to-reach hepatitis C patients who were lost to follow-up: A qualitative study. *PLoS One.* 2020;15(4):e0230756.
14. Litwin AH, Drolet M, Nwankwo C, Torrens M, Kastelic A, Walcher S, et al. Perceived barriers related to testing, management and treatment of HCV infection among physicians prescribing opioid agonist therapy: The C-SCOPE Study. *J Viral Hepat.* 2019;26(9):1094-104.
15. Treloar C, Newland J, Rance J, Hopwood M. Uptake and delivery of hepatitis C treatment in opiate substitution treatment: perceptions of clients and health professionals. *J Viral Hepat.* 2010;17(12):839-44.
16. VKN. 2025 [Available from: <https://verslavingskundenederland.nl/we-are-daa/>].
17. HepNed. 2025 [Available from: <https://hepned.nl/>].
18. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* 2007;19(6):349-57.

19. Schatz E. IDPC Briefing Paper The Dutch treatment and social support system for drug users. International Drug Policy Consortium. 2011.
20. Nationale Drug Monitor. Opiaten 5.6 Hulpvraag en incidenten - Nationale Drug Monitor: Trimbos-instituut, Utrecht & WODC, Den Haag; 2022 [Available from: <https://www.nationaledrugmonitor.nl/opiaten-hulpvraag-en-incidenten/>].
21. Von den Hoff DW, Berden FAC, Drenth JPH, Schellekens AFA, HepNed N. Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care. Study protocol for the Hepatitis C: chain of addiction care (CAC) project. *Addict Sci Clin Pract*. 2022;17(1):67.
22. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3(2):77-101.
23. Hart W. *Verdraaide organisaties*. first edition ed. Amsterdam: Boom; 2012.
24. Bredenberg E, Callister C, Dafoe A, Holliman BD, Rowan SE, Calcatera SL. Subspecialty physicians' perspectives on barriers and facilitators of hepatitis C treatment: a qualitative study. *Harm Reduct J*. 2024;21(1):140.
25. Phillips C, Schulkind J, O'Sullivan M, Edelman N, Smith HE, Verma S, et al. Improving access to care for people who inject drugs: Qualitative evaluation of project ITTREAT-An integrated community hepatitis C service. *J Viral Hepat*. 2020;27(2):176-87.
26. Zgierska AE, Miller MM, Rabago DP, Hilliard F, McCarthy P, Cowan P, et al. Language Matters: It Is Time We Change How We Talk About Addiction and its Treatment. *J Addict Med*. 2021;15(1):10-2.
27. Helsper CW, Janssen MP, van Essen GA, Croes EA, van der Veen C, de Wit AG, et al. Effectiveness and cost-effectiveness of nationwide campaigns for awareness and case finding of hepatitis C targeted at people who inject drugs and the general population in the Netherlands. *Int J Drug Policy*. 2017;47:117-25.
28. Hogenbirk. RIVM National Hepatitis Plan. 2016.
29. Solomon SS, Wagner-Cardoso S, Smeaton L, Sowah LA, Wimbish C, Robbins G, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2022;7(4):307-17.
30. Lai JC, Liang LY, Wong GL. Noninvasive tests for liver fibrosis in 2024: are there different scales for different diseases? *Gastroenterol Rep (Oxf)*. 2024;12:goae024.
31. Goodyear T, Brown H, Browne AJ, Hoong P, Ti L, Knight R. "I want to get better, but...": identifying the perceptions and experiences of people who inject drugs with respect to evolving hepatitis C virus treatments. *Int J Equity Health*. 2021;20(1):81.
32. Assoumou SA, Sian CR, Gebel CM, Linas BP, Samet JH, Bernstein JA. Patients at a drug detoxification center share perspectives on how to increase hepatitis C treatment uptake: A qualitative study. *Drug Alcohol Depend*. 2021;220:108526.
33. WHO. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. 2022.

Supplementary files

Topic list

General Information:

- Age of the interviewee
- Current position
- Years of experience in the field
- Explanation of the term "Chain of Addiction Care" (CAC) regarding hepatitis C care decentralization

Knowledge Assessment:

- Self-assessment of hepatitis C knowledge (epidemiology, pathology, treatment, prognosis)
- Perception of colleagues' knowledge (patient care level)
- Perception of colleagues' knowledge (organizational/decision-making level)
- Additional factors influencing hepatitis C knowledge

Role of the Institution:

- Role of the addiction care institution in hepatitis C diagnosis, treatment, and follow-up
- Satisfaction with the institution's hepatitis C care delivery
- Perspectives on fully decentralized hepatitis C care within the institution

Chain of Addiction Care (CAC) Experience:

- Participation in the CAC project
- Experience with CAC implementation

Facilitators and Barriers for CAC Implementation:

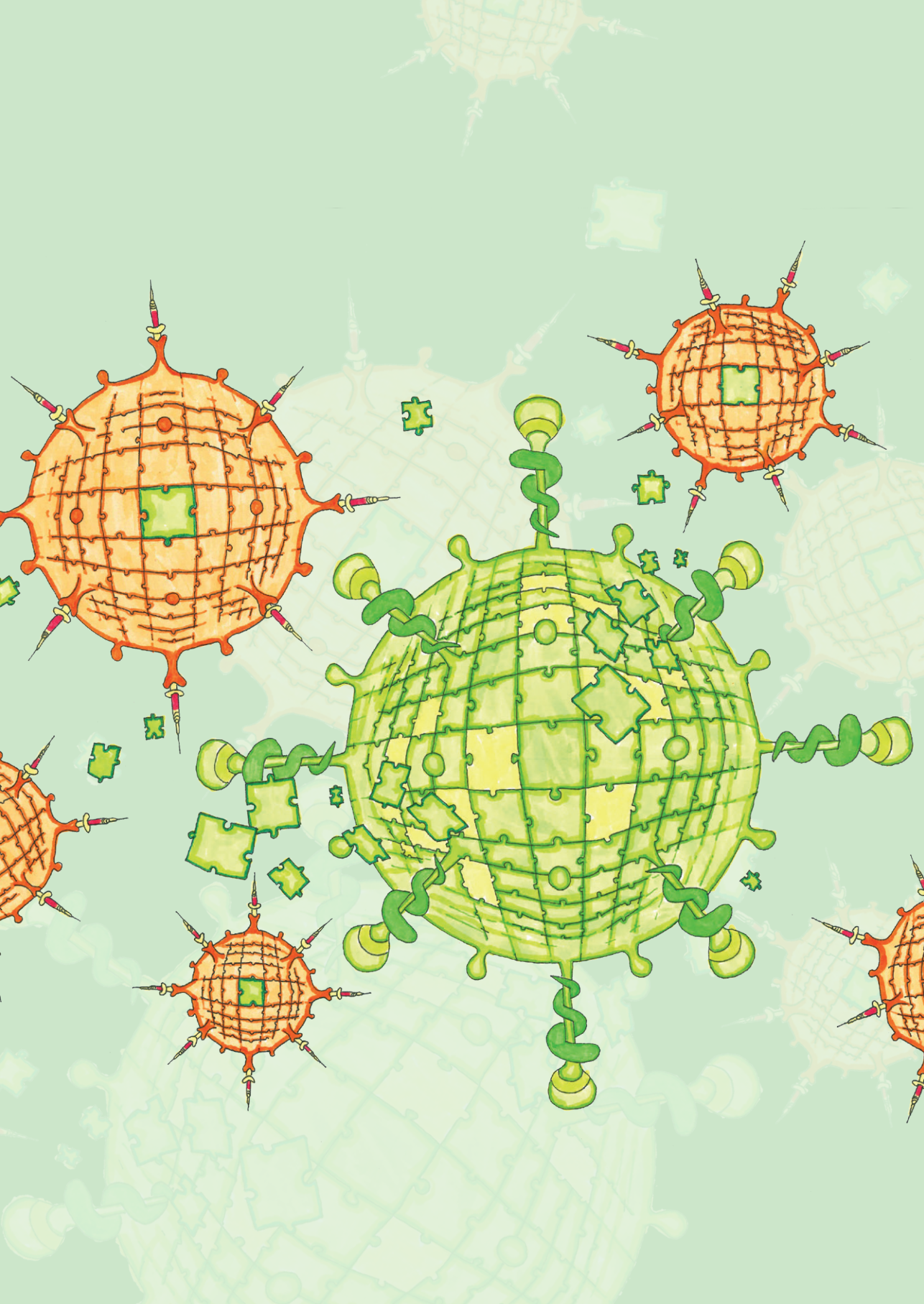
- Patient level
- Healthcare provider level
- Administrative level
- Other potential levels

Views on Centralized vs. Decentralized Care:

- Opinion on fully centralized hepatitis C care
- Expected future barriers to decentralization
- Prioritization of key barriers to address

Final Remarks:

- Additional comments or questions from the interviewee
- Follow-up requests regarding study results



Chapter 7

General Discussion

The central aim of this thesis was to provide actionable insights into how addiction care can contribute to the effort toward worldwide hepatitis C virus (HCV) elimination. Addiction and HCV are two conditions intricately woven together, which require an integrated approach. The introduction of direct acting antivirals (DAAs) has revolutionized management of HCV. However, due to population specific factors and a hospital focused care, people who use(d) drugs (PWUD) have not been able to fully profit from advancements in HCV management up to now. In this thesis we studied interactions between addiction and, we evaluated the implementation of the Hepatitis C: Chain of Addiction Care (CAC), a decentralized HCV care model embedded in addiction services. Overall, with this thesis we set out to contribute to existing literature by highlighting implementation insights and future research directions, with the ultimate goal of advancing the broader public health goal of HCV elimination.

Findings

Part one: addiction and hepatitis C, two interacting conditions

We performed a claims data study exploring the association between a history of addiction and suboptimal hospital-based HCV care. Contrary to prevailing assumptions, we observed in **chapter 2** that in the Netherlands, PWUD demonstrated better overall utilization of hepatitis-related hospital care compared to the general population (1-4). However, overall optimal HCV healthcare utilization was low. Only: 47% of referred patients received what was defined as optimal viral hepatitis care within the first year following referral. An exploratory analysis revealed that people with a migration background were significantly more likely to receive suboptimal care, possibly due to language and insurance issues (5, 6). Due to the nature of claims data, HCV patients who did not receive any hospital care were not represented in this study. A study by van Dijk et al. reported that 73% of Dutch patients lost to follow-up in the HCV care cascade had a history of substance use, and 30% of those relinked to care presented with advanced fibrosis, underscoring the clinical consequences of inadequate linkage to care and follow-up (7). Taken together, these findings suggest that addiction history is not in itself a barrier to optimal hospital-based viral hepatitis care once the patient accesses the hospital, but that suboptimal care in general is prevalent.

Chapter 3 explored the effect of hepatitis C cure on methadone pharmacokinetics. Four patients on opioid agonist therapy (OAT) with methadone were monitored for plasma levels before and after succesful HCV treatment. Two patients showed

a marked decrease in dose-normalized methadone concentrations post-treatment in line with our hypothesis. In two other patients, HCV treatment did not affect methadone plasma levels. Although one patient showed a decrease in one methadone enantiomer and an increase in the other. These findings suggest interindividual variability in methadone metabolism, which has been described before(8, 9). In our study with only a few patients however, we have not been able to control for other possible mechanisms at play, as methadone undergoes complex, partly nonlinear kinetics influenced by variability in absorption as well as hepatic metabolism and renal excretion(8, 9). Future studies should further explore the hypothesis that reduced hepatic inflammation can result in improvement of CYP activity after HCV sustained virologic response (SVR).

Part two: implementing decentralized hepatitis C care in Dutch addiction care

We evaluated CAC by taking into account varying dimensions of implementation using quantitative and qualitative methods on organizational, healthcare provider and patient level. The development and implementation strategy for CAC was introduced in **chapter 4**. Recognizing the multidimensional nature of implementation, a combined quantitative and qualitative study based on the RE-AIM model (Reach, Effectiveness, Adoption, Implementation, Maintenance) was proposed (10-12). With our studies we aimed to capture not only clinical outcomes, such as SVR and elimination rates, but also system-level factors and staff engagement. Chapter 4 outlines the study protocol for the evaluation described in chapters 5 and 6.

The prospective, multicenter study presented in **chapter 5** demonstrated that the CAC model is both feasible and clinically effective. Among HCV-RNA positive individuals enrolled across participating addiction care centers, 86% achieved SVR, a viral elimination rate comparable to or exceeding that reported in controlled trials and international community-based programs (13-15). Every patient that started treatment and was tested for SVR, achieved SVR, in line with high SVR rates (>95%) described in literature (16). Treatment was provided on-site by addiction care staff, without the need for hospital-based care in the majority of cases (88%), three patients had to be referred to the hospital due to comorbid conditions as determined in the protocol. Despite its clinical success, adoption of the CAC model was moderate. Only five out of eleven addiction care organizations implemented the pathway during the study period. This indicates that broader system-level uptake remains a key challenge for scale-up. The implementation study conducted as part of this thesis was observational in nature and did not include a comparison group, which limits the ability to draw causal conclusions. Nonetheless, the use

of the RE-AIM framework provided a structured lens through which to assess the model's performance across multiple dimensions even though the "Maintenance" component could not be evaluated within the available study period.

The barriers and facilitators of decentralized HCV care within Dutch addiction care were explored in **chapter 6**, through qualitative interviews with all stakeholders such as addiction care professionals, outpatient HCV specialists and policymakers. Patiënt viewpoints were studied extensively elsewhere. Thematic analysis identified a range of facilitators, such as the role of nurses, patient familiarity and trust in addiction care staff, and increased treatment adherence through decentralization. Participants also highlighted the importance of a referral and consultation network with the local hospital. Barriers included slow decision-making on the organizational level in large addiction care centers, limited financial and personnel resources, and low HCV prevalence hindering expertise development. Importantly, the decentralized care model was positively received by participants.

Reflection

The close interconnection between addiction and HCV remains evident following the findings of this thesis. At the same time, the findings in **chapter 2** demonstrate that addiction does not inherently imply suboptimal HCV care. By showing this, the present work may contribute to reducing persistent stigma surrounding addiction within healthcare contexts. If HCV care for high-risk populations is to be organized within hospital settings at all, other groups may warrant increased attention, such as individuals with a migration background. Organizing HCV care for PWUD in the hospital is called into question by the low overall rates of optimal care observed in this chapter and in contrast to the success of CAC. A major strength of the use of claims data lies in the ability to analyze healthcare utilization patterns at the population level within a representative cohort. However, claims data are inherently limited by underdocumentation, a lack of clinical detail (such as fibrosis staging), and the potential misclassification of diagnoses. As HCV care for PWUD in the Netherlands is increasingly shifting toward a decentralized model, future large-scale data studies may be more feasibly conducted through existing national addiction care networks, such as NISPA and Verslavingskunde Nederland (VKN).

In **chapter 3**, this thesis explores a novel frontier in the interaction between HCV and addiction by examining potential effects of HCV cure on methadone pharmacokinetics, an area in which no prior *in vivo* studies were available. Given the small sample size and the various methodological limitations, strong conclusions

Overview of aims, main findings and limitations			
#	Research aims	Main Findings	Limitations
PART 1	2 To evaluate whether a medical history of an addictive disorder is associated with suboptimal hospital hepatitis healthcare utilization.	- Contrary to assumptions, PWUD showed better utilization of hospital hepatitis care than the general population. - Only 47% received “optimal care” within one year of referral. - People with a migration background were at higher risk for suboptimal care.	- Definition of “optimal care” was pragmatic, not validated. - Claims data lacked clinical detail and may suffer from misclassification. - Patients not accessing hospital care were not represented.
	3 To determine the effect of HCV cure on methadone pharmacokinetics.	- In two of four patients, HCV cure led to a decrease in methadone concentrations. - In two others, no significant effect was observed, suggesting interindividual variability.	- Very small sample size (n=4) limits generalizability - Exploratory findings should be interpreted cautiously.
PART 2	4 To describe the methods, the project and the RE-AIM dimensions of CAC*.	A mixed-methods evaluation protocol based on the RE-AIM framework was developed, capturing clinical, system-level, and organizational outcomes.	- Preparatory work only; framework was applied in later chapters. - Long-term maintenance could not yet be evaluated.
	5 To quantitatively evaluate the organizational and patient dynamics of the implementation of CAC*.	- The CAC model was feasible and clinically effective. 86% of HCV-RNA positive patients achieved SVR comparable to international results. - Care was largely delivered on-site by addiction care staff. - Moderate adoption, 5/11 centers implemented the model.	- Observational study without control group limits causal inference. - The number of patients identified was relatively low.
	6 To identify the facilitators and barriers to implementing HCV care in addiction care.	- Facilitators: trust in addiction staff, role of nurses, enthusiasm, and collaboration with hospitals. - Barriers: slow organizational decision-making, resource constraints, low HCV prevalence limiting expertise.	- Findings context-specific to Dutch addiction services; - Generalizability and long-term integration uncertain.

*Hepatitis C Chain of Addiction Care, the HCV care decentralization effort in the Netherlands
SVR=Sustained virological response.

are not warranted. Therefore, the results should be interpreted with caution and replicated in future studies using more rigorous and experimental designs. Nonetheless, this interaction is noteworthy, particularly in the HCV field which is often regarded as largely exhausted of new frontiers. The clinical relevance remains to be established and should preferably be investigated in larger, controlled studies. Such studies could clarify whether standardized adjustments in methadone dosing are clinically necessary during and after HCV treatment, thereby enhancing patient safety and stability in opioid agonist therapy. Even if this interaction proves to be of limited relevance for HCV specifically, similar mechanisms may apply to other forms of liver inflammation. Given that methadone is frequently prescribed for long-term or lifelong use, this line of research remains relevant and should not be overlooked.

The CAC model's implementation was evaluated in **chapters 5 and 6**. It constitutes a practice-driven, guideline-informed approach to decentralizing HCV care, specifically adapted to the structure and workflow of Dutch addiction care. We believe this led to its high success rate and operational fit within existing clinical routines. Addiction care thus proved to be a particularly suitable context for HCV management, facilitated by its longstanding familiarity with the target population, the presence of low-threshold access, and established therapeutic relationships. At the same time, the implementation experience highlighted broader structural challenges. The frequently reported financial and personnel constraints limit addiction care to perform tasks that are not aligned with its primary objective (treating addiction). We may see the consequences of that in the relatively low number of identified HCV patients and the low participation rate of organizations overall. This might ultimately stem from a separation of somatic and mental healthcare, which in The Netherlands is still visible in its insurance structure (DBC vs. zorgprestatie model).

At the same time, participating sites have shown that with low time investment, high health benefit can be achieved. Although HCV prevalence may be low, addiction care staff reported that HCV diagnosis and treatment were generally straightforward and could often be delivered by specialized nurses. This strengthens the rationale for a simple, clearly defined clinical guideline, as developed within CAC (see appendix). It should also be mentioned that although the CAC model was developed with considerable care at the time of its conception, it is important to acknowledge that additional effective interventions have been found in the meantime. The findings of Cunningham et al. support the established superiority of integrated approaches, however they also discovered other interventions to be effective, such as medical chart reminders, dried blood spot testing, opt-out

screening, and patient education (13, 17). These were not integrated in the CAC pathway and may further improve future efforts to decentralize HCV care. A study by Bredenberg et al. underscores the added value of multidisciplinary teams, including pharmacists and patient navigators, elements not formally integrated into CAC, but probably relevant for future refinement in the Dutch context (18). This suggestion was also done by participants in chapter 6. Further refinement may be gained from minimal treatment monitoring approaches; emerging literature suggests substituting scheduled visits for remote contact, which may also be viable in PWUD populations, potentially simplifying care delivery even further (19).

Several methodological considerations regarding the evaluation of CAC warrant further reflection. The use of the RE-AIM framework for implementation evaluation proved intuitive and comprehensive, offering a structured approach to assessing multiple dimensions of real-world impact beyond clinical effectiveness alone. Nevertheless, alternative implementation frameworks, such as the Consolidated Framework for Implementation Research (CFIR) or Normalization Process Theory (NPT), may have provided alternative insights into organizational dynamics. A notable limitation of the present implementation evaluation is that the Maintenance dimension of RE-AIM could not be assessed within the available study period. Long-term sustainability, scalability, and system-level impact therefore remain uncertain and warrant future investigation through larger, longitudinal studies. Such research will be essential to determine whether the CAC model can be maintained over time, scaled up to a national level, and adapted to evolving healthcare structures. Finally, while the CAC model was specifically designed for and evaluated within the Dutch addiction care system, the extent to which it can be replicated or adapted to other healthcare contexts remains unclear. Differences in funding structures, professional roles, and the organization of addiction and somatic care may influence transferability.

Towards hepatitis C elimination

Taken together, the work presented in this thesis has several implications for the future organization of HCV care and for research at the intersection of HCV and addiction care. Decentralized models embedded within addiction care are capable of delivering substantial health gains with relatively limited time investment, challenging the necessity of hospital-centered approaches for PWUD. Addiction care, due to its accessibility, multidisciplinary character, and pre-existing relationship with PWUD, is well-positioned to serve as the cornerstone for HCV

care (figure 1). Therefore, the new Dutch view on HCV care for PWUD should be addiction care centered, with hepatitis experts taking on a consultation role while open to referral in case of complex comorbidity. As a first step, a dedicated module for HCV diagnosis and treatment within addiction care has been incorporated into the national ‘Dutch HCV guidance’ <https://hcvrichtsnoer.nl/verslavingszorg/>(20). It was inspired by the CAC workflow and emphasizes a low-threshold, pragmatic approach that prioritizes accessibility, flexibility, and continuity of care as is also supported by international guidelines (16, 21). New policy and alternative resource allocation are required to facilitate adoption of this approach. For instance, successful decentralization requires structural support like financial reimbursement for somatic medicine in mental healthcare, staff HCV training and supervision, improved electronic patient data infrastructure, and clear local protocols for execution and for collaboration with specialist care. Without such system-level adaptations, decentralization efforts risk not being adopted or being unsustainable.

The WHO elimination goals for 2030 are rapidly approaching and CAC findings have shown that addiction care is already able to manifest high elimination rates with current resources. Therefore a call to action is in order. This call is aimed at addiction care staff, including nurses, as our findings show that nurses may be able to play a vital role in managing HCV. They have easy access to the patient and are well equipped to perform standardized HCV treatment.

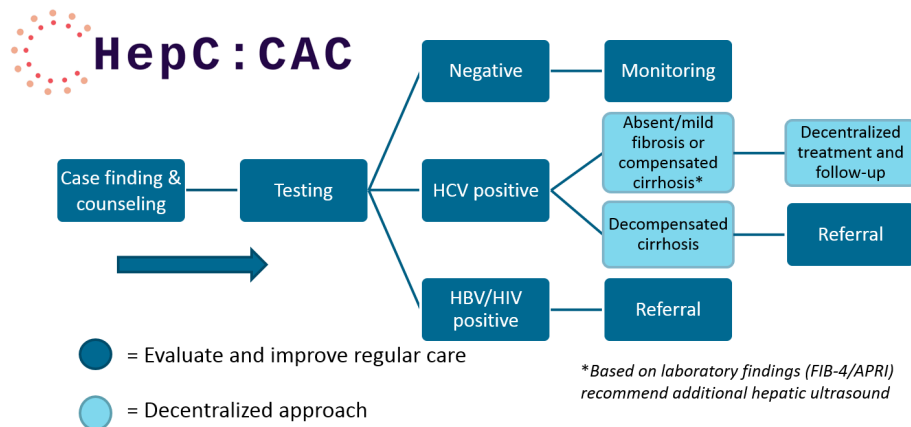


Figure 1. Simplified suggested pathway for PWUD at risk for HCV in addiction care

This thesis has identified several research areas requiring further investigation to sustain progress towards HCV elimination among PWUD. Firstly, while CAC demonstrated strong clinical effectiveness, adoption was lacking and maintenance was not studied. Aforementioned policy interventions might lead to increased uptake of decentralized HCV models in organizations that have not taken part yet, strengthening adoption.

Maintenance however is a topic that requires further studies, as it remains unclear whether the decentralized approach in participating centers is durable, and which factors influence this. Expansion to additional centers and evaluation of maintenance may warrant a second iteration of CAC. We also recommend further evaluation of the pharmacokinetic interaction between HCV clearance and methadone metabolism. Our study was limited by small patient numbers and uncontrolled factors. Future studies should include larger numbers to robustly quantify changes in CYP enzyme activity and should also include controlled methadone dosing, intake time, assessment of CYP polymorphisms, monitoring of concomitant medication and substance use, and standardized measures of craving.

Concluding remarks

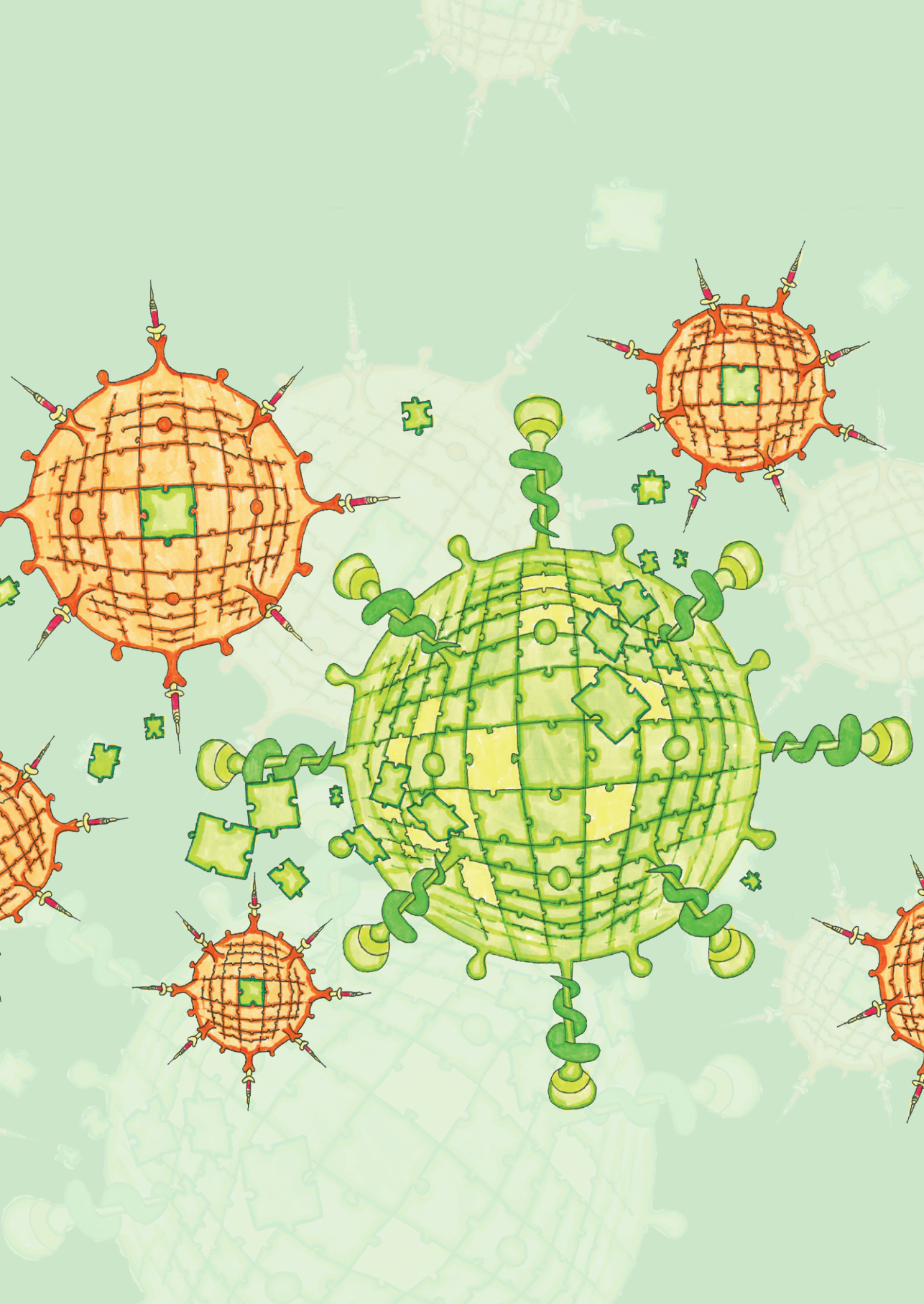
The main conclusions from this thesis are summarized as follows:

- Substance use itself is not a barrier to optimal HCV care once patients receive hospital-based care. (chapter 2).
- A possible interaction exists between successful HCV treatment and methadone metabolism, necessitating further investigation to substantiate this finding and to identify clinical relevance (chapter 3).
- Decentralized hepatitis C care within addiction care is both clinically effective and practically feasible, achieving elimination rates (86%) comparable to international standards (chapter 5).
- Integrated HCV-addiction care was enthusiastically received. Facilitators and barriers on the organizational-, staff-, patient- and treatment level influence successful implementation and can be used to improve local HCV management in addiction care (chapter 6).
- The combined qualitative and quantitative implementation evaluation, guided by the RE-AIM framework, offered a comprehensive assessment of both well-performing dimensions (reach, effectiveness) and areas requiring further improvement (adoption, maintenance) (chapters 4, 5 and 6).

References

1. Nitulescu R, Young J, Saeed S, Cooper C, Cox J, Martel-Laferrriere V, et al. Variation in hepatitis C virus treatment uptake between Canadian centres in the era of direct-acting antivirals. *Int J Drug Policy*. 2019;65:41-9.
2. Solund C, Hallager S, Pedersen MS, Fahnoe U, Ernst A, Krarup HB, et al. Direct acting antiviral treatment of chronic hepatitis C in Denmark: factors associated with and barriers to treatment initiation. *Scand J Gastroenterol*. 2018;53(7):849-56.
3. Hajarizadeh B, Cunningham EB, Reid H, Law M, Dore GJ, Grebely J. Direct-acting antiviral treatment for hepatitis C among people who use or inject drugs: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*. 2018;3(11):754-67.
4. van Dijk M, Drenth JPH, HepNed study g. Loss to follow-up in the hepatitis C care cascade: A substantial problem but opportunity for micro-elimination. *J Viral Hepat*. 2020;27(12):1270-83.
5. Kim JU, Ingiliz P, Shimakawa Y, Lemoine M. Improving care of migrants is key for viral hepatitis elimination in Europe. *Bull World Health Organ*. 2021;99(4):280-6.
6. Seedat F, Hargreaves S, Nellums LB, Ouyang J, Brown M, Friedland JS. How effective are approaches to migrant screening for infectious diseases in Europe? A systematic review. *The Lancet Infectious Diseases*. 2018;18(9):e259-e71.
7. Isfordink CJ, van Dijk M, Brakenhoff SM, Kracht PAM, Arends JE, de Knecht RJ, et al. Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination. *Eur J Intern Med*. 2022.
8. Eap CB. Interindividual Variability of the Clinical Pharmacokinetics of Methadone. *Clinical Pharmacokinetics*. 2012;Volume 41.
9. Hanna J, Foster DJ, Salter A, Somogyi AA, White JM, Bochner F. Within- and between- subject variability in methadone pharmacokinetics and pharmacodynamics in methadone maintenance subjects. *Br J Clin Pharmacol*. 2005;60(4):404-13.
10. Glasgow RE, Harden SM, Gaglio B, Rabin B, Smith ML, Porter GC, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. *Front Public Health*. 2019;7:64.
11. Holtrop JS, Estabrooks PA, Gaglio B, Harden SM, Kessler RS, King DK, et al. Understanding and applying the RE-AIM framework: Clarifications and resources. *J Clin Transl Sci*. 2021;5(1):e126.
12. Sweet SN, Ginis KA, Estabrooks PA, Latimer-Cheung AE. Operationalizing the RE-AIM framework to evaluate the impact of multi-sector partnerships. *Implement Sci*. 2014;9:74.
13. Oru E, Trickey A, Shirali R, Kanter S, Easterbrook P. Decentralisation, integration, and task-shifting in hepatitis C virus infection testing and treatment: a global systematic review and meta-analysis. *The Lancet Global Health*. 2021;9(4):e431-e45.
14. Wade AJ, Doyle JS, Gane E, Stedman C, Draper B, Iser D, et al. Outcomes of Treatment for Hepatitis C in Primary Care, Compared to Hospital-based Care: A Randomized, Controlled Trial in People Who Inject Drugs. *Clin Infect Dis*. 2020;70(9):1900-6.
15. Fadnes LT, Aas CF, Vold JH, Leiva RA, Ohldieck C, Chalabianloo F, et al. Integrated treatment of hepatitis C virus infection among people who inject drugs: A multicenter randomized controlled trial (INTRO-HCV). *PLoS Med*. 2021;18(6):e1003653.
16. EASL eee, Clinical Practice Guidelines Panel C, representative EGB, Panel m. EASL recommendations on treatment of hepatitis C: Final update of the series(). *J Hepatol*. 2020;73(5):1170-218.

17. Cunningham EB, Wheeler A, Hajarizadeh B, French CE, Roche R, Marshall AD, et al. Interventions to enhance testing, linkage to care, and treatment initiation for hepatitis C virus infection: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7(5):426-45.
18. Bredenberg E, Callister C, Dafoe A, Holliman BD, Rowan SE, Calcaterra SL. Subspecialty physicians' perspectives on barriers and facilitators of hepatitis C treatment: a qualitative study. *Harm Reduct J*. 2024;21(1):140.
19. Solomon SS, Wagner-Cardoso S, Smeaton L, Sowah LA, Wimbish C, Robbins G, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2022;7(4):307-17.
20. Hepatitis C Richtsnoer (dutch guideline) [Available from: <https://hcvrichtsnoer.nl/>].
21. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology*. 2020;71(2):686-721.



Chapter 8

Appendices

Summary

Summary in Dutch

About the author

List of Publications

Research data management

PhD Portfolio

Dankwoord (Acknowledgments)

Summary

This thesis focused on *two main pillars*: 1) the interaction between addiction and the hepatitis C virus (HCV), and 2) how to improve HCV management for people who use or have used drugs. The underlying premise is that addiction care, where many of these patients are already engaged, can serve as an important point of access to reach, test, and treat this population. In this way, addiction care can contribute to the broader objective of the World Health Organization (WHO): the elimination of hepatitis C as a global public health threat.

In the *first part* of this thesis, the relationship between addiction and hepatitis C was further explored. **Chapter 2** examined whether individuals with a history of addiction in the Netherlands received poorer hospital-based care for hepatitis C compared to the general population. This was not the case. On the contrary, once these patients accessed hospital care, they on average made greater use of hepatitis-related services. However, the study also showed that less than half of all referred patients received the care considered necessary by specialists within one year. In particular, individuals with a migration background more often received suboptimal care. These findings indicate that it is not addiction history itself that limits access to adequate care, but rather that linking patients to care and retaining them in care remains a major challenge. **Chapter 3** investigated changes in methadone levels in the blood of patients undergoing treatment for hepatitis C. Methadone is commonly used as maintenance therapy for individuals with opioid dependence, such as heroin use. Because hepatitis C affects the liver, and the liver plays a key role in drug metabolism, it was examined whether HCV cure alters methadone metabolism. In two of the four patients, methadone levels clearly decreased after treatment, possibly reflecting improved CYP function following viral clearance. In the other two patients, no changes were observed. This small study highlights interindividual variability and indicates that larger, well-controlled follow-up studies are needed to better understand whether these changes have clinical implications for the treatment of HCV and/or addiction.

The *second part* of this thesis addressed the organization of care: how can we improve hepatitis C management? In the Netherlands, treatment is usually provided in hospital settings, often by hepatologists or infectious disease specialists. For people who use(d) drugs, accessing hospital care can represent a substantial barrier. Therefore, the Hepatitis C: Chain of Addiction Care (CAC) project was developed, in which care is organized within the familiar setting of addiction services as much as possible. **Chapter 4** described how this project was evaluated,

using the RE-AIM framework. This framework not only considers clinical outcomes, but also addresses questions such as: how many people are reached, how well the approach works in practice, how widely it is adopted, and whether it can be sustained over time. In **Chapter 5**, the effectiveness of this model was evaluated in practice. Across multiple addiction care centers, patients were tested and treated for hepatitis C, often by their own care providers. Among those who were HCV-RNA positive, 86% achieved SVR. This outcome is comparable to, or even better than, results reported in international studies and hospital settings. Importantly, most treatments were delivered entirely within addiction care, without the need for hospital visits. At the same time, the study showed that only a subset of organizations implemented the model: five out of eleven centers participated. This indicates that scaling up and broader implementation is needed. **Chapter 6** therefore explored which factors facilitated or hindered the implementation of this care model. Interviews were conducted with addiction care professionals, hospital specialists, and policymakers. Facilitators included the high level of trust patients place in their addiction care providers, and the good fit of the model within existing workflows. The role of nurses within addiction care was also identified as crucial. At the same time, important barriers were identified, such as slow decision-making processes in large organizations, limited financial and personnel resources, and the decreasing prevalence of HCV, which may reduce opportunities to build and maintain expertise. Overall, the new approach was perceived by stakeholders as valuable and well-aligned with daily practice.

The central message of this thesis is that addiction care represents a strong platform for improving access to and delivery of HCV management. The CAC model has demonstrated that providing treatment within the patient's familiar environment is not only feasible, but also as effective as hospital-based care, with the added advantage of better alignment with the patient. Addiction itself therefore does not need to be a barrier to high-quality HCV care. However, broader and sustainable implementation requires structural adaptations, including wider adoption, appropriate funding, targeted training, and clear collaboration agreements with hospital services. The findings of this thesis underline that addiction care is not only a setting for the treatment of substance use disorders, but can also function as a gateway to improved physical health and the prevention of serious conditions such as HCV. This work contributes to the ambition of eradicating HCV in the Netherlands and abroad.

Summary in Dutch

Dit proefschrift richtte zich op *twee belangrijke pijlers*: 1) de wisselwerking tussen verslaving en hepatitis C virus (HCV) en 2) hoe de behandeling van HCV beter kan worden georganiseerd voor mensen die drugs gebruiken of hebben gebruikt. Het uitgangspunt is dat de verslavingszorg, waar veel van deze patiënten in zorg zijn, een belangrijk toegangspunt kan zijn om hen te bereiken, te testen en te behandelen. Op die manier kan de verslavingszorg bijdragen aan de bredere doelstelling van de Wereldgezondheidsorganisatie (WHO): het elimineren van hepatitis C als wereldwijd gezondheidsprobleem.

In het *eerste deel* van dit proefschrift werd de samenhang tussen verslaving en hepatitis C verder onderzocht. In **hoofdstuk 2** is nagegaan of mensen met een voorgeschiedenis van verslaving in Nederland slechtere ziekenhuiszorg kregen voor hepatitis B en C dan de algemene bevolking. Dat bleek niet het geval te zijn. Integendeel, zodra deze patiënten eenmaal in het ziekenhuis terechtkwamen, maakten zij gemiddeld zelfs meer gebruik van hepatitis-gerelateerde zorg. Toch liet het onderzoek zien dat minder dan de helft van alle verwezen patiënten binnen een jaar de zorg kreeg die volgens specialisten noodzakelijk is. Vooral mensen met een migratieachtergrond ontvingen vaker minder goede zorg. Deze bevindingen maken duidelijk dat het niet de verslavingsachtergrond zelf is die goede zorg in de weg staat, maar dat het koppelen van patiënten aan zorg en het vasthouden daarvan een groot knelpunt vormt. In **hoofdstuk 3** werd gekeken naar wat er gebeurt met de methadonspiegels in het bloed van patiënten die een behandeling voor hepatitis C ondergaan. Methadon is een medicijn dat vaak gebruikt wordt bij een onderhoudsbehandeling voor mensen met een verslaving aan opioïden zoals heroïne. Omdat hepatitis C invloed heeft op de lever, en de lever belangrijk is voor de afbraak van medicijnen, werd onderzocht of de genezing van hepatitis C ook de verwerking van methadon verandert. Bij twee van de vier patiënten daalden de methadonspiegels duidelijk na de behandeling, wat mogelijk komt doordat de leverfunctie na genezing verbeterde. Bij de andere twee patiënten veranderde er niets. Deze kleine studie laat zien dat er verschillen bestaan tussen mensen, en dat groter en beter gecontroleerd vervolgonderzoek nodig is om beter te begrijpen of dit in de praktijk gevolgen heeft voor de behandeling van HCV dan wel verslaving.

Het *tweede deel* van dit proefschrift ging over het verbeteren van de organisatie van zorg: hoe kan de behandeling van hepatitis C dichterbij de patiënt worden gebracht? In Nederland vindt behandeling normaal gesproken plaats in het ziekenhuis, vaak bij een maag-, darm- en leverarts of infectioloog. Voor mensen

die drugs gebruiken kan die stap naar het ziekenhuis groot zijn. Daarom werd het project *Hepatitis C: Chain of Addiction Care* (CAC) ontwikkeld, waarbij de zorg zoveel mogelijk binnen de vertrouwde setting van de verslavingszorg zelf wordt georganiseerd. In **hoofdstuk 4** werd beschreven hoe dit project zou worden geëvalueerd. Daarbij is gebruikgemaakt van een raamwerk (RE-AIM) dat niet alleen kijkt naar medische resultaten, maar ook naar vragen als: hoeveel mensen bereik je, hoe goed werkt de aanpak in de praktijk, hoeveel organisaties nemen het over, en is de aanpak vol te houden op de lange termijn. In **hoofdstuk 5** werd de effectiviteit van dit model onderzocht in de praktijk. In meerdere verslavingszorginstellingen werden patiënten getest en behandeld voor hepatitis C, vaak door het eigen personeel. Van de patiënten die daadwerkelijk geïnfecteerd waren met het virus, genas 86% volledig. Dit resultaat is vergelijkbaar met of zelfs beter dan wat in internationale onderzoeken en ziekenhuizen wordt gezien. Belangrijk was dat de meeste behandelingen geheel binnen de verslavingszorg plaatsvonden, zonder dat een bezoek aan het ziekenhuis nodig was. Tegelijkertijd liet dit onderzoek zien dat slechts een deel van de instellingen het model daadwerkelijk invoerde: vijf van de elf organisaties deden mee. Dit wijst erop dat het opschalen en breder invoeren van het model niet vanzelf gaat. Daarom werd in **hoofdstuk 6** onderzocht welke factoren het implementeren van dit zorgmodel makkelijker of juist moeilijker maakten. Hiervoor werden interviewsuitgevoerd met zorgverleners en beleidsmakers van de verslavingszorg en specialisten uit het ziekenhuis. Positieve punten waren dat patiënten veel vertrouwen hebben in hun vaste begeleiders in de verslavingszorg, en dat het zorgmodel goed aansloot bij bestaande werkprocessen. Ook de rol van verpleegkundigen in de verslavingszorg bleek cruciaal. Tegelijkertijd waren er belangrijke barrières, zoals trage besluitvorming in grote organisaties, een tekort aan geld en personeel, en het feit dat HCV steeds minder voorkomt waardoor instellingen minder ervaring opbouwen. Al met al werd de nieuwe aanpak door de betrokkenen als waardevol en passend ervaren.

De kernboodschap van dit proefschrift is dat de verslavingszorg een krachtig platform vormt om mensen met een verslavingsachtergrond én beter te bereiken en succesvol te behandelen. Het CAC-model heeft aangetoond dat behandeling in de vertrouwde omgeving van de patiënt niet alleen haalbaar is, maar ook even effectief als ziekenhuiszorg, met bovendien het voordeel dat het beter aansluit bij de leefwereld van de patiënt. Een verslaving hoeft op zichzelf dus geen belemmering te zijn voor goede HCV zorg. Voor brede en duurzame toepassing zijn echter structurele aanpassingen nodig, zoals bredere implementatie, passende financiering, gerichte scholing en heldere samenwerkingsafspraken met ziekenhuizen. De bevindingen van dit proefschrift onderstrepen dat de verslavings-

zorg niet uitsluitend een plek is voor behandeling van middelengebruik, maar tevens kan fungeren als opstap tot betere lichamelijke gezondheid en preventie van ernstige aandoeningen zoals HCV. Daarmee draagt dit proefschrift bij aan de ambitie om HCV in Nederland en daarbuiten verder terug te dringen.

About the author

Nederlands

Daan Willem Von den Hoff werd geboren op 27 december 1993. Hij groeide op met zijn ouders Hans, Carol en Paul, samen met zijn jongere broer Tim en zusje Sofie. In 2012 behaalde hij zijn gymnasiumdiploma aan het Dominicus College in Nijmegen, waarna hij startte met de studie Geneeskunde, eveneens in Nijmegen.

Tijdens zijn studententijd leidde hij een actief en veelzijdig leven, onder andere bij roeivereniging Phocas, waar hij zich ook een jaar bestuurlijk inzette. In de masterfase van zijn studie ontwikkelde hij een bijzondere interesse in maag-, darm- en leverziekten. Hij liep een seniorcoschap op de afdeling Maag-, Darm- en Leverziekten in het Jeroen Bosch Ziekenhuis en verrichtte een onderzoeksstage in Milaan, gericht op oesofagusstenose. In deze periode ontstond tevens zijn relatie met zijn partner Myrthe.

Na het behalen van zijn artsenbul in 2019 startte hij direct met een promotietraject, gericht op de implementatie van hepatitis C-zorg binnen de verslavingszorg, onder leiding van prof. dr. J.P.H. Drenth, promotor prof. dr. A.F.A. Schellekens en co-promotor dr. F.A.C. Berden. Tijdens zijn promotie werkte hij daarnaast als arts binnen de verslavingszorg bij Iriszorg in Ede, zowel op de polikliniek als in het ambulante team. Hier groeide zijn interesse in verslaving en psychiatrie. In 2024 werd zijn zoon Abel geboren. Gedreven door zijn klinische- en wetenschapservaringen koos hij er na afronding van het grootste deel van zijn promotietraject voor om zich verder te ontwikkelen binnen de psychiatrie. Hij startte als arts op de afdeling psychiatrie van het Radboudumc, waar hij momenteel in opleiding is tot psychiater. In 2026 werd zijn dochter Saar geboren.

English

Daan Willem Von den Hoff was born on December 27, 1993. He grew up with his parents, Hans, Carol, and Paul, together with his younger brother Tim and sister Sofie. In 2012, he graduated from the Dominicus College in Nijmegen, after which he started medical school at the Radboud University in Nijmegen.

During his student years, he led an active and diverse life, including his involvement in the rowing association Phocas, where he also completed a board year. During the clinical phase of his training, he developed a particular interest in gastroenterology and hepatology. He completed a senior internship at the Department of Gastroenterology and Hepatology at the Jeroen Bosch Hospital and conducted a research internship in Milan focusing on esophageal stenosis. During this period, he also began his relationship with his partner, Myrthe.

After obtaining his medical degree in 2019, he immediately started his PhD project, focusing on the implementation of hepatitis C care within addiction services, under the supervision of Prof. J.P.H. Drenth, Prof. A.F.A. Schellekens and co-supervisor Dr. F.A.C. Berden. During his PhD, he also worked as a physician in addiction care at Iriszorg in Ede, both in outpatient clinics and in community-based teams. This experience strengthened his interest in addiction medicine and psychiatry. In 2024, his son Abel was born. Motivated by his clinical experiences, and after completing most of his PhD, he decided to further specialize in psychiatry. He started working as a physician at the Department of Psychiatry of the Radboud University Medical Center, where he is currently in training to become a psychiatrist. In 2026, his daughter Saar was born.

List of Publications

If the mountain won't come to Mohammed, then Mohammed must go to the mountain: Decentralisation of hepatitis C care for people who use drugs

Year: 2021

Journal: *United European Gastroenterology Journal*

Authors: D.W. Von den Hoff, F.A.C. Berden, A.F.A. Schellekens

DOI: 10.1002/ueg2.12167

Against All Odds? Addiction History Associated with Better Viral Hepatitis Care: A Dutch Nationwide Claims Data Study

Year: 2022

Journal: *Journal of Clinical Medicine*

Authors: D.W. Von den Hoff, F.A.C. Berden, F. Atsma, A.F.A. Schellekens, J.P.H. Drenth

DOI: 10.3390/jcm11041146

Implementation of a decentralized hepatitis C care pathway for people who use drugs in Dutch addiction care: Study protocol for the Hepatitis C: Chain of Addiction Care (CAC) project

Year: 2022

Journal: *Addiction Science & Clinical Practice*

Authors: D.W. Von den Hoff, F.A.C. Berden, J.P.H. Drenth, A.F.A. Schellekens

DOI: 10.1186/s13722-022-00350-1

Hepatitis C-virusbehandeling met direct-werkende antivirale middelen in de verslavingszorg

Year: 2022

Journal: *Psyfar* (Educational Article)

Authors: D.W. Von den Hoff, F.A.C. Berden, E.J. Smolders

Facilitators and barriers for implementation of a decentralized hepatitis C care chain for people who use drugs in Dutch addiction care

Year: 2024

Journal: *Drug and Alcohol Dependence*

Authors: D.W. Von den Hoff, H. Ellerbroek, J.P.H. Drenth, F.A.C. Berden, A.F.A. Schellekens

DOI: 10.1016/j.drugalcdep.2025.112759

Successful hepatitis C elimination through decentralized treatment in Dutch addiction care: A RE-AIM based evaluation

Year: 2025

Journal: *Drug and Alcohol Dependence*

Authors: D.W. Von den Hoff, F.A.C. Berden, A Noordeloos, T Knuijver, ` A.F.A. Schellekens, J.P.H. Drenth.

DOI: 10.1016/j.drugalcdep.2025.113014

The impact of Hepatitis C Cure on Methadone Pharmacokinetics: A Case Series

Year: 2026 (expected)

Authors: D.W. Von den Hoff, E.J. Smolders, F.A.C. Berden, D.M. Burger, S. Hegstad, O. Spigset, J.P.H. Drenth, A.F.A. Schellekens.

In preparation

Research Data Management

Ethics and Privacy

This thesis is based on the results of research involving human participants. The studies were conducted in accordance with relevant national and international legislation, regulations, guidelines, codes of conduct, and Radboudumc policy. A statement was obtained from the recognized Medical Ethics Review Committee *METC Oost-Nederland* confirming that the relevant subprojects were not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) (file numbers: 2019-5939 and 2022-13584).

The privacy of participants was safeguarded in accordance with Dutch and European data protection legislation. For the **chapters 3, 5 and 6**, the privacy of the participants was warranted by pseudonymization. Each participant was assigned a unique study code, while the pseudonymization key was stored separately on secure servers at the participating addiction care centers, accessible only to designated investigators. For **chapter 2**, no informed consent was required since only anonymized nationwide claims data were analyzed. Written informed consent was obtained from participants in all other studies, covering both participation and the use of data for future research. Where applicable, participants were asked to indicate whether they consented to the sharing and reuse of pseudonymized data according to the FAIR principles.

Data Collection and Storage

Data collection followed a structured approach tailored to the needs of each study.

- **Chapter 2:** Data were based on existing nationwide hospital claims datasets (2012–2019) obtained from Statistics Netherlands (CBS). These microdata files consisted of anonymized diagnostic and treatment codes. Access to these data was arranged via a CBS data access agreement, which specifies conditions for use and restrictions on data sharing.
- **Chapter 3 and 5:** Data were prospectively collected using electronic Case Report Forms (eCRF) in Castor EDC. Clinical and demographic data were entered directly into Castor EDC by trained personnel. The datasets were subsequently exported to SPSS for analysis.
- **Chapter 6:** Qualitative interview data were collected using secured electronic devices and, demographics were pseudonymized at source.

All raw data were first stored securely on the Radboudumc department server during the data collection phase. After completion of the collection, data were archived

in the Radboud Data Repository. Raw data files were preserved in DAC/DSC, while processed data and accompanying documentation (protocols, codebooks, syntaxes, software versions, and readme files) were stored in Research Documentation Collections (RDC). These secure storage options safeguard the availability, integrity, and confidentiality of the data throughout the project lifecycle.

Availability of Data

In line with the FAIR principles, data availability was carefully considered for each subproject.

- **Chapter 2:** Data underlying this study cannot be shared. The dataset is owned by Statistics Netherlands (CBS) and subject to strict confidentiality agreements. Access to the data can only be granted by CBS under specific conditions and is not transferable.
- **Chapter 3 and 5:** Pseudonymized datasets will be archived in the Radboud Data Repository under restricted access. Requests for access will be reviewed by the principal investigator in accordance with the signed informed consent and formalized through a Data Use Agreement (DUA).
- **Chapter 6:** Interview transcripts will be archived in the Radboud Data Repository under closed access.

All datasets are stored in preferred interoperable formats (CSV, SPS, XML, PDF) to ensure long-term accessibility. Metadata, including study protocols, codebooks, and SPSS syntaxes, are added to enable reuse and verification. Each dataset archived in the Radboud Data Repository receives a persistent identifier (DOI), ensuring findability (see table). Thus, data from these studies will be made “as open as possible, as restricted as necessary,” balancing the FAIR principles with the ethical and legal responsibility to protect the privacy of study participants.

identifiers: *ru.rumc.hepccac_t0000598a_dac_400*, *ru.rumc.hepccac_t0000598a_rdc_011*, *ru.rumc.hepccac_t0000598a_dsc_166*

Chapter	Repository	Collection Type	Access & License / DUA
2	Statistics Netherlands (CBS)	Not applicable	Closed access; CBS data access agreement required
3	Radboud Data Repository	DSC	Restricted access; DUA required
5	Radboud Data Repository	DSC	Restricted access; DUA required
6	Radboud Data Repository	DAC & RDC	Closed access

PhD Portfolio

Department: Gastroenterology and Hepatology

PhD period: 1st December 2019 - 30th September 2023

PhD Supervisor: Prof. dr. J.P.H. Drenth

PhD Co-supervisor(s): Prof. dr. A.F.A. Schellekens, Dr. F.A.C. Berden

Training activities	Hours
Courses	
• Radboudumc – Introduction day (2020)	6
• RIMLS – “In the lead” Introduction course for PhD candidates (2020)	15
• Radboudumc - eBROK course (2021)	42
• Radboudumc - Scientific integrity (2022)	20
• Radboudumc - Qualitative research course (2021)	30
• Radboudumc- Motivational interviewing (2021)	36
• Voice and presentation training by Debby Mureau	8
Seminars	
• GI-Hep meetings with Research experts (2020-2023)	10
• Research Integrity rounds (2021)	1,5
• Research Integrity rounds (2022)	1,5
• Soeterbeeck regional GI seminars (2020-2023)	21
Conferences	
• Digestive disease days, virtual (2020)	16
• Digestive disease days, Veldhoven (2022)	16
• Digestive disease days, Veldhoven (2023); incl. poster presentation	16
• RIMLS Retreat New Frontiers (2023); incl. oral presentation	8
• IVHEM 2020 virtual; incl. oral presentaton	20
• Wetenschappelijk Middagprogramma Haaglanden (2021); oral presentation	5
• NISPA-dag 2021; incl. oral presentation	8
• NISPA-dag 2022	8
• NISPA-dag 2023; incl. oral presentation	8
• NISPA-dag 2024	8
• INHSU Glasgow 2022	24
• HepNed symposium (2020)	8
• HepNed Symposium (2022); incl. organization and oral presentation	8
• UEG Week Copenhagen 2023; incl. poster presentation	24
• Jaarsymposium Verslaving 2023; incl. oral presentation	8

Training activities	Hours
Other	
• Journal club Department of Gastroenterology and Hepatology (2020-2023)	188
• Research meeting Gastroenterology and Hepatology (2022-2024)	188
• NISPA forum (2020-2023)	40
• NISPA writing retreats (2020-2024)	120
Teaching activities	
• Radboudumc basis klinisch onderwijs (BKO)	75
Supervision of internships	
• Supervision research internship (Master Medicine) – Miran Mahmoud (2021)	28
Total	1015

Dankwoord

Joost, hartelijk dank voor de fijne begeleiding. Ik heb de afgelopen jaren geen moment het gevoel gehad dat ik niet op je kon terugvallen als dat nodig was. Je was altijd beschikbaar voor scherpe feedback of een gevatte kijk op een moeilijk probleem. Ik denk dat dit product er niet was geweest, of tenminste pas veel later, als ik niet steeds jouw gepaste druk om de eindstreep te gaan halen had gevoeld. Ondanks dat ik soms het koppie even kon laten hangen bleef je me altijd op een prettige manier aanmoedigen en dat waardeer ik enorm. **Arnt**, jij had hier net zo goed bovenaan kunnen staan, ontzettend bedankt voor de begeleiding. Jouw passie voor onderzoek, kundigheid en enthousiasme over welk onderwerp dan ook maakte dat ik steeds na onze afspraken weer met frisse moed de volgende stap kon zetten. Daarnaast waardeer ik dat toen ik begon te twifelen over mijn toekomstpad je ook klaarstond om me daarbij te ondersteunen en dat heeft mede gemaakt dat ik nu met veel plezier de Psychiatrie opleiding volg. **Floor**, wat fijn dat jij de rol van co-promotor wilde vervullen. Jouw kritische blik, volledigheid en oog voor detail zijn onmisbaar geweest. Ik denk dat jij precies aanvulde wat ik soms miste als ik weer te snel wilde gaan. Vele uren vrije tijd heb je geïnvesteerd in sparsessies, mijn kromme teksten doorakkerend, en als eerste hulp als ik het even niet meer zag zitten. Dankjewel daarvoor!

Ik bedank graag **Abbvie** en **Gilead** voor het financieel mogelijk maken van mijn promotieonderzoek en de verschillende afgevaardigden die daarbij hebben ondersteund.

Mijn dank gaat verder uit naar alle verslavingsartsen, verpleegkundigen en ander ondersteunend personeel van deelnemende verslavingsinstellingen die deze uitdaging met mij hebben willen aangaan. Het viel soms niet mee om dit project langs de verschillende lagen van de organisatie, onderzoekscommissies en autoriteitenfiguren te loodsen, laat staan de uitvoering van de zorg- en onderzoekstaken zelf. Ik ben heel blij dat jullie ook het belang van optimale hepatitis zorg hebben ingezien en je hiervoor hebben willen inzetten. In het bijzonder noem ik graag nog **Annemarie** en **Thomas**, die tevens nog een belangrijke rol hebben willen spelen in het vormgeven van het project en schrijven van een manuscript. Verder bedank ik natuurlijk ook de patiënten die hebben willen deelnemen.

De collega's van **HepNed**, **NISPA**, en **IQHealthcare** die ik over de jaren om advies heb mogen vragen wil ik ook graag bedanken, net als het ondersteunend personeel van de **afdeling MDL** en van NISPA voor het organiseren van de basisfaciliteiten die promoveren überhaupt mogelijk maken.

Graag bedank ik ook de leden van de manuscriptcommissie **prof. dr. R.B. Kool**, **prof. dr. M. van der Valk** en **dr. B.A.G. Dijkstra** voor de tijd en energie die u gestoken heeft in het kritisch beoordelen van mijn proefschrift.

Beste collega (arts-)onderzoekers van de afdeling MDL en van NISPA: **Ayla, Britt, Christa, Dorien, Edo, Elsa, Fenna, Fenna, Gijs, Jasmijn, Julia, Kelly, Koen, Lia, Lieke, Lisa, Lotte, Lucas, Maarten, Marleen, Melissa, Menso, Michiel, Mike, Milou, Monica, Naomi, Pepijn, Renée, Romée, Sabien, Thijs, Veerle, Yonne, Amber, Arno, Boukje, Casper, Debbie, Elise, Femke, Hannah, Harmen, Lisa, Lianne, Maarten, Stijn, Wiebren**, ondanks COVID-perikelen heb ik mede door jullie allemaal een hele fijne promotietijd gehad. Wat waren jullie een prettig gezelschap tijdens alle journal clubs, fora, lunchpauzes, koffiemomentjes, congressen, borrels, schrijfretraites en weekendjes weg. Tezamen hebben jullie met de eindeloze verhalen en leuke momenten mijn werk leuk gemaakt. Het reikt te ver om iedereen individueel te bedanken, maar dat maakt mijn dank niet minder groot! Ik noem wel graag nog mijn waardige voorgangster op hepatitis C **Marleen**, bedankt voor de vliegende start die ik door jou heb kunnen maken. **Maarten**, we hebben gegamed, we hebben bier gedronken, we hebben geproost op jouw verbintenis met Maja en we zien kleine Nora opgroeien, wat fijn dat ik jou door deze promotie tegen het lijf ben gelopen! **Thijs**, ik heb geworsteld met mijn rol als onderzoeker en in jou zag ik de échte onderzoeker en hoe dat samen kon gaan met gewoon een hele leuke vent zijn. Bedankt! **Monica**, wij hebben samen de grootste poging gedaan om de feesten en borrels waarheid te maken, ik zie je op DTRH! **Hannah**, bedankt voor de gezelligheid op zo'n beetje elke NISPA activiteit waar ik was. En hoewel hepatitis C helemaal niet jouw ding was heb je mij willen helpen mijn interviews te analyseren en het manuscript te schrijven, eeuwig dank daarvoor!

Elise, bedankt voor je samenwerking bij het schrijven van ons nascholingsartikel in Psyfar en voor je hulp bij het project dat het meest ver-van-mijn-bed-show is, die wordt nog gepubliceerd hoor!

Collega's van de **psychiatrie** in het **Radboud** en **Rijnstate**, jullie bedank ik graag voor de laatste jaren waarin jullie hebben meegekregen hoe bij mij de laatste loodjes vielen. Jullie hebben me opgevangen, aangehoord en gemotiveerd, waarvoor dank. In het bijzonder bedank ik alle supervisoren en de opleiders **Daphne, Philip en Jeroen**, voor het meedenken in het organiseren van ruimte in mijn opleiding voor het tot een goed einde kunnen brengen van mijn promotie. Dat jullie dit lezen betekent dat ik veel aan jullie ondersteuning heb gehad!

Ik ben gezegend met een legio vrienden, zonder wie ik nooit de mentale kracht had kunnen opbrengen om door te gaan en deze promotie tot een goed einde te brengen. Allereerst de mooie heren van onze reünistenvereniging Centurio: **Auke, Didi, Jan Douwe, Jasper, Kees, Leon, Niek, Olmo, Simon, Tom, Toon, Tycho, Victor, Vincent, Wietze**. Zonder jullie veel minder hoogtepunten in mijn leven, die hoogtepunten die ik zo heb gewaardeerd de afgelopen jaren. Denk aan weekenden, festivals, uitjes, borrels, etentjes en spelletjesavonden. Verder de mensen waarmee ik het meest intensieve jaar van mijn leven heb mogen meemaken tijdens mijn bestuursjaar van Phocas, het 69e: **Niek, Karlijn, Bob, Tamar, Donald, Elske en Anne**, we hebben nooit lang nodig om weer in oude patronen te vervallen. Roeien doet 50/50 allang niet meer, maar festivallen, weekendjes weg, dineren en kerst vieren blijven we altijd doen hè **Anton, Jorn, Tycho en Thomas**. Wat velen niet zullen toegeven maar wat zeker bij een onderzoeker past is je nerderige kant laten zien. De afgelopen jaren heb ik me kunnen verliezen in verschillende alter-ego's in Dungeons and Dragons. Bedankt voor de avonturen die voor de nodige afleiding hebben gezorgd **Lukas, Thomas, Maikel, Naud, Iris en Bodil**.

Tych, om jou kan ik het hardst lachen en ik heb altijd het gevoel dat ik je te weinig zie en spreek. Gelukkig komt daar een einde aan, hopelijk binnenkort. Zo, nu staat het zwart op wit. Bedankt voor je steun en vriendschap! **Lukas**, jouw grappen zijn ingestudeerd en ik ken ze allemaal, maar toch blijf ik erom lachen. Jouw oprechtheid en intense overgave maken elke biertje of spelletje een feest. Je zit met Melissa aan de andere kant van de wereld waar jullie mooi en belangrijk werk doen, beetje balen dat je er niet bent. **Wietze**, we eten kip en we gamen. Je helpt me als ik weer eens moet verhuizen of verbouwen. Je vraagt vaak "is die promotie nou al af?": "ja, nu wel". Soms hoeft het ook niet zo ingewikkeld te zijn. Bedankt dat je mijn paranimf wil zijn. **Thomas**, geef ons een biertje en een spelletje en de uren vliegen voorbij. Dat hoeven we niemand uit te leggen. Wij hebben sinds onze studententijd alle grote momenten samen gedeeld en dat wil ik ook graag blijven doen. Met Amber zette jij Sam op de wereld en nu delen we ook het vaderschap. Nu sta je hier natuurlijk ook naast me.

Vaders jij bent de eerste Dr. Von den Hoff, en ik ben trots dat ik de tweede mag zijn. Hoewel ik waarschijnlijk nooit jouw impact op onderzoeksgebied ga maken weet ik dat je onwijs trots op me bent. **Moeders** jij bent er altijd en overal voor mij geweest. Het gaat me niet altijd even makkelijk af om om hulp te vragen dus gelukkig kan ik op jouw hulp vanzelfsprekend rekenen, dankjewel. **Paul**, jouw rust, steun en aanwezigheid hebben meer betekend dan ik vaak onder woorden breng. **Tim en Fie**, mijn liefste broertje en zusje, iedereen kan aan ons zien dat wij

een hechte band hebben, die is en blijft enorm belangrijk voor mij. **Juliëtte** en **Diony**, dank voor jullie betrokkenheid, op de oppasdinsdagen kon ik altijd wel een geïnteresseerde vraag van jullie verwachten. Verder bedank ik natuurlijk ook graag mijn overige (schoon)familie voor alle steun.

Voordat ik de laatste woorden van dank uitspreek wil ik graag zeggen dat er nog velen anderen zijn die het verdienen hier benoemd te worden, omdat ze op wat voor manier dan ook betrokken zijn geweest bij mij of mijn werk als promovendus, daarom ook voor u: **hartelijk dank!**

Tot slot, mijn prachtige gezin, waar ik het allemaal voor heb gedaan en nog steeds doe. **Saar**, je bent nog niet lang in ons leven, maar je bent mooier dan ik had durven dromen. Als ik jou zie verdwijnen even al mijn zorgen. Ik ben zo benieuwd naar hoe je gaat opgroeien. **Abel**, jouw enthousiasme en gevoel voor humor dat je met je twee levensjaren al hebt, maakt dat ik zoveel mogelijk thuis wil zijn. Dat heeft mijn promotie ongetwijfeld verlengd maar het was het waard kleine man! Lieve **Myrthe**, mijn leuke, gekke, creatieve, knappe, zorgzame levenspartner. Bedankt dat je altijd in me bent blijven geloven en me liefdevol weer op het juiste pad duwde als ik het even niet meer zag zitten. Ik denk dat jij tenminste zo blij bent als ik dat we dit hoofdstuk nu kunnen afsluiten, al heb je dat nooit hardop gezegd. Jij brengt de kleur in mijn leven, ik hou van je.

