Going HCVree

Prevention of hepatitis C reinfection in HIV-infected men who have sex with men

A mixed methods study to enable scalability of a behavioral risk reduction intervention

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List of Abbreviations

ART	Antiretroviral Therapy
CI	Confidence Interval
CISS	Computer-assisted Intervention for Safer Sex
CM	Crystal Methamphetamine
DAA	Direct Acting Antivirals
EBI	Evidence-Based Intervention
EMIS	European MSM Internet Survey
GHB/GBL	γ-butyrolactone/γ-hydroxybutyric acid
HCPs	Health Care Providers
HCV	Hepatitis C Virus
HET	Heterosexual
IDU	Injection Drug Use
IM	Intervention Mapping
IMB	Information-Motivation-Behavioral skills model
IQR	Interquartile Range
MI	Motivational Interviewing techniques
MRC	Medical Research Council
nsCAI	Condomless Anal Intercourse with non-steady partners
OR	Odds Ratio
OST	Opioid Substitution Therapy
PrEP	Pre-Exposure Prophylaxis
py	person years
RCT	Randomized Controlled Trial
SCT	Social Cognitive Theory
SD	Standard Deviation
SDU	Sexualized Drug Use
SHCS	Swiss HIV Cohort Study
STIs	Sexually Transmitted Infections
SVR	Sustained Viral Response
TIDieR	Template for Intervention Description and Replication
TTM	Transtheoretical Model
UK	United Kingdom
WHO	World Health Organization

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Summary

Since the introduction of highly effective direct-acting antivirals (DAA), elimination of the hepatitis C virus (HCV) has become a realistic objective, leading the World Health Organization (WHO) to define elimination goals by 2030 [1]. Because HCV incidence and prevalence are more relevant within certain groups [2], focusing on key subpopulations for micro-elimination can be an effective strategy [3].

This requires the development of interventions tailored specifically for the target groups. In addition to screening and providing access to treatment, the overall intervention plan has to include the prevention not only of new infections but also of reinfection [3, 4].

In high-income countries, HIV-infected men who have sex with men (MSM) represent a high-impact treatment group. In recent years, members of this group have showed rapidly increasing HCV incidence. For example, an 18-fold increase was observed between 1998 and 2011 in MSM participating in the Swiss HIV Cohort Study (SHCS) [5].

A major trigger for this HCV epidemic in HIV-infected MSM is sexual transmission. While related biological, behavioral and social factors are all discussed, behavioral factors appear to be the most important drivers of transmission [6, 7]. Sexual practices that put MSM particularly at risk are currently a matter of discussion. For example, sexualized drug use is associated with additional risks, e.g., sharing of injection equipment or sexual encounters with increased potential for anal or rectal trauma [8-12]. And while some discussion remains as to the exact ranking of transmission drivers, current evidence indicates that an interplay between sexual and drug use behaviors is extremely influential [13].

Among HIV-infected MSM, the incidence-rate of HCV reinfection after successful treatment—5.93-9.2/100 person-years (py)—is the highest of any current grouping [14, 15]. Considering that reinfection is associated with complex behavioral risk factors, successful micro-elimination will demand a combination of behavior change and medical treatment as numerous researchers have argued [13, 16-18].

In 2015, noting the urgent need to prevent HCV reinfection in HIV-infected MSM, Swiss researchers decided to test an approach that combined pharmaceutical treatment with a behavioral counselling intervention [19]. Their decision was supported by a mathematic modelling study indicating that, without behavioral changes, micro-elimination would not be possible in Switzerland [20]. Until that time, no behavioral intervention focusing on HCV-related sexual risk reduction has been described or evaluated; five years later, to our knowledge, this is the first such study.

The overall immediate aim of this thesis was to strengthen the comprehensive behavioral prevention strategy, with the long-term aim of improving HCV micro-elimination. Guided by the Medical Research Council (MRC) *framework for complex interventions in health* [21, 22] in our process's first phase, we developed an HCV-specific sexual risk reduction intervention by adapting an evidence-based HIV sexual risk reduction intervention. In the second, after feasibility testing the resulting intervention within the framework of the Swiss HCVree Trial, we evaluated its impact.

Chapter 1 provides an introduction to our topic in terms of content and methodology. Its first part focuses on HCV elimination and the strategies necessary to achieve that goal; the second presents arguments supporting our approach and choice of methods.

Chapter 2 presents our goals.

MRC framework phase I

Chapter 3 describes our development of a behavioral counselling intervention. We worked with the concept of scaling-out, i.e., the process of improving the intervention's fit to a new context while maintaining its effectiveness [23]. This approach was influenced by our increased awareness of implementation research and the importance of "putting evidence into practice" [24]. The adaptation process was guided by the Intervention Mapping (IM) Adapt approach [25] and a contextual analysis. At many steps, broad stakeholder involvement helped us discover the needed changes. The adapted intervention was called *HCVree and me*.

MRC framework Phase II

The project's second phase focused on the evaluation of the *HCVree and me* feasibility test. We were especially interested in how the intervention worked in practice and to use this knowledge for further improvement when considering scalability [26, 27]. We used mixed methods, with methods chosen as appropriate for each evaluation question [26].

In the Swiss HCVree Trial, the decision was made to invite only men who reported inconsistent condom use with non-steady partners (nsCAI) in the previous year. In **chapter 4**, we examined the appropriateness of using this selection criterion for the behavioral intervention in 118 of our 122-man sample. We analyzed their self-reported sexual and drug use behaviors at baseline. While 72 (61%) qualified for the intervention, other potential HCV transmission risk behaviors were also frequent, e.g., 52 (44%) had used drugs, 44 (37%) reported sexualized drug use and 17 (14%) had injected drugs. This finding highlighted that the chosen screening question had excluded numerous men who indicated a need to develop prevention-centered behaviors.

Chapter 5 reports the results of a qualitative study in the behavioral intervention's participants. For this, our aim was to understand the intervention program's meaning for participants regarding their sexuality and risk behaviors. One-third of participants (n=17) agreed to semi-structured interviews. The narratives revealed one constitutive theme: *Giving hepatitis C a place and living without it again*, illustrating first how participants positioned themselves to the program and thereafter their sense-making work in relation to it.

All participants responded to the intervention program, but with considerable variation. Therefore, we differentiated three sense-making work: *Avoid risks: get rid of hepatitis C for life; Minimize risks: live as long as possible without hepatitis C;* and *Accept risk: live with the risk of hepatitis C.* This work summed up not only the range of the participants' various responses to the intervention but also their later management of sexual risks. Also, regardless of their responses to the behavioral counselling intervention, the results also revealed that treatment had had a significant influence on their sense-making.

The fourth article, described in **chapter 6,** built on these sense-making groups. This study's aim was to validate that the three groups also differed in the content of sexual risk reduction goal-setting and behavior change. To achieve this, we conducted a convergent mixed-method study. The qualitative analysis identified seven domains reflecting broader risk reduction strategies; the quantitative analysis largely supported the differentiation of the groups. The merged data validated our hypothesis. This finding is important because the qualitatively generated sense-making work groups can now be used to inform further intervention development and tailoring. However, the analysis also indicated that our quantitative instrument was sub-optimal for measuring initiated diverse risk reduction strategies and emphasizes the need for better outcome variables/questionnaire items.

Chapter 7 presents a synthesis and discussion of the results, particularly three key findings. We begin by describing how the innovative combination of traditional and newer implementation frameworks facilitated the intervention's successful scaling-out. Following the feasibility test, we identified and described the participants' various responses regarding their sense-making work. The resulting groups reflected the diversity of their experiences with both the behavioral intervention and the DAA treatment. The chapter ends with an explanation of how the participants' dynamic sexual behavior influenced not only our interpretation of evaluation findings but also the need for further adaptations to the intervention.

These studies' findings highlighted various implications for future research and clinical practice. As a next step, we recommend revising the intervention according to the results of our evaluation, then preparing for the next trial—particularly to better cover sexualized drug use behaviors. For clinical practice, we recommend encouraging joint discussion within clinical teams to raise awareness of potential reinfection-related stigma, of assessment of problematic sexualized drug use behaviors and of how to use clinical appointments as teachable moments. This will certainly impact patient-centered care and will very likely also improve patient outcomes.

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Chapter 1. Background

1.1 Introduction

The effectiveness of direct-acting antivirals has prompted the WHO to set 2030 as their target year for HCV elimination [1]. However, treatment alone will not lead to success. What is needed is a combination of strategies including screening, access to treatment and prevention not only of new infections but of reinfection, as HCV treatment gives no immunity [2].

To facilitate progress, many countries have developed programs targeting specific high-impact populations [3]. People living with HIV are one such population: HCV is six times more prevalent in HIV-positive people than in their HIV-negative counterparts [4]. However, this group is by no means homogeneous. For example, HIV-infected MSM show an even higher HCV prevalence (3-39%), with the majority of new HCV infections occurring in those who engage in high-risk sexual behavior [5]. This tendency was also observed in an analysis of the Swiss HIV Cohort Study (SHCS) [6].

In 2015, the Swiss HCVree Trial was launched. Its immediate aim was to investigate the impact of micro-elimination using a test-treat-cure-and-counsel strategy on HCV prevalence in HIV/HCV co-infected MSM; over a longer term, its aim was to interrupt HCV transmission in HIV-infected MSM [7]. The argument for integrating a behavioral counselling intervention into the trial was based on the results of mathematical modelling studies [8, 9] showing that without sexual risk reduction micro-elimination would not be possible.

This conclusion has since been confirmed by the results of numerous DAA studies in the HIV field. While cure rates were very high (e.g., 92% in a Spanish study with HIV/HCV co-infected people) [10], HIV-positive men showed increased rates of reinfection, emphasizing the need for comprehensive prevention strategies [11, 12].

In 2015, when we began development of the Swiss HCVree Trial, to our knowledge, in the context of HCV prevention, no other behavioral counselling intervention was described for the specific needs of HIV/HCV co-infected MSM. Therefore, the overall aim of this thesis was to strengthen the comprehensive reinfection prevention strategy by improving micro-elimination. In the first phase, we adapted an evidence-based HIV prevention intervention for use within a systematic HCV prevention program. In the second, we evaluated the impact of this new intervention on HIV-infected MSM.

1.2 Hepatitis C Virus and elimination efforts

Chronic HCV is a potentially fatal blood-borne virus with a worldwide prevalence of 2.3% [13] although this varies considerably across regions and populations [14]. In 2013, HCV infections became a leading cause of mortality worldwide [15]. In Switzerland, it is estimated that roughly 40'000 people were living with HCV in 2014 [16], with HCV showing a mortality rate six times that of HIV or hepatitis B virus [17].

Since then, the introduction of well-tolerated, effective DAA—with cure rates of over 95%—[18] has changed HCV from a lifelong chronic condition to one for which eradication is a realistic possibility. The WHO's global HCV elimination goal 2030 includes reductions of 80% for new HCV infections and of 65% for mortality [1]. To reach these goals, screening and access to treatment are essential; however, as no vaccine yet exists, the prevention of new infections is equally essential, but far more complex [3, 19].

For every step mentioned thus far, then, major barriers stand between the WHO and their goals. First, screening is difficult because HCV is a "silent disease", i.e., many of those infected are unaware because they have no symptoms and health care practitioners (HCPs) do not test without an obvious or known past risk situation [2]. Therefore, some countries, e.g., the Unites States [20], have introduced universal or birth-cohort screening; others, e.g., Canada [21] and various European countries [2], use risk-based screening.

The second major barrier is limited access to treatment. In the beginning, high drug prices prompted many countries both in Europe (> 50%) and in North America to impose restrictions on treatment [22]. This was also the main reason why, until 2017, Switzerland only reimbursed patients with advanced liver disease for their DAA. Linas et al. [23] argued that this decision was often based primarily on treatment costs and not on cost-effectiveness. For Switzerland, two cost-effectiveness studies identified the impact of treatment on liver-related burden and mortality [24, 25]. Since October 2017, treatment has been available to all HCV-infected people in Switzerland and covered under the national health insurance program.

Next to finances, another significant barrier is that many physicians hesitate to treat current drug users because they anticipate, e.g., adherence problems or MSM because of ongoing sexual risk taking, e.g. problem of reinfection [5, 22]. However, as recreational drug use and high-risk sexual activities—are often practiced by the same people—carry a high risk of disease transmission, both signal an urgent need not only for treatment but, even more importantly, for preventive measures [23].

Treatment alone leads to only moderate success. As an elimination approach, its sustainability is limited if not alloyed with prevention strategies—a principle abundantly clear in people who inject drugs. A 2019 modelling study indicated that scaled-up treatment has a stronger impact when combined with effective harm reduction services (e.g., opioid substitution treatment (OST) or syringe service programs). Together, both strategies can reduce HCV incidence and prevalence. In contrast, without full harm reduction, twice as many therapies will eventually be needed [26]. Australian studies in drug users who receive OST showed that community-based approaches worked well in strengthening testing [27] or facilitating treatment completion (e.g. 96% of 127 participants) [28].

Based on these findings, Hellard et al. [29] recommended that actively engaging people who inject drugs is the most effective strategy to strengthen efforts in testing, treating and prevention. The same findings indicate the importance of coordinated multi-level activities regarding treatment and prevention needs within defined groups.

In such defined sub-populations, micro-elimination can facilitate scale-up activities very well. While allowing researchers to tailor their efforts precisely to the target group's needs, it supports proactive planning and coordination of prevention activities [3, 30].

People living with HIV are a population that would benefit strongly from increased efforts because HIV/HCV co-infection show a higher risk for liver-related morbidity and mortality [4, 31, 32]. Successful treatment carries numerous benefits. Not only does it lead to longer survival, significant reduction of liver cirrhosis, improved quality of life, and reduced morbidity, it also prevents extrahepatic complications in this population [16, 33-35].

Some countries make the results of micro-elimination programs in people with HIV available. One example is Australia, which tested a treatment-as-prevention strategy promoting unlimited treatment uptake in people living with HIV. The results included a significant reduction of HCV co-infection [36].

Regarding micro-elimination within the overall group of people living with HIV, MSM build an important sub-group: as noted above, most new HCV infections occur in HIV-infected MSM who engage in high-risk sexual behavior. One review showed an international HCV prevalence of 3-39% in HIV-infected MSM (HIV-negative MSM 0-19%) and an increasing incidence of 2.34-5.11/100py already in 2007 [5].

Similar data apply to Switzerland. Between 1998 and 2011, the SHCS noted an 18-fold increase of HCV incidence in HIV-infected MSM, indicating a "changing epidemic," i.e., one shifting from HIV-infected people who inject drugs to HIV-infected MSM [6] (see figure 1). This shift occurred because implementation of harm reduction strategies

successfully reduced the incidence of HCV infection in people who inject drugs; the increasing incidence in HIV-infected MSM is mainly due to sexual transmission [34].

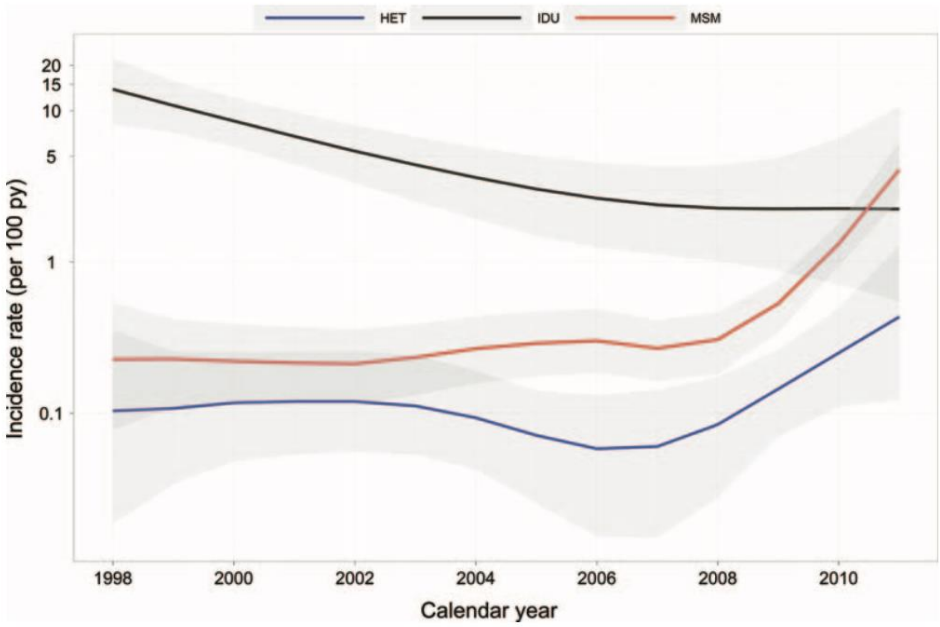

Figure 1: Hepatitis C virus infection incidence-rates per 100 person-years (py) by transmission group (shaded: 95% credible intervals) in the Swiss HIV Cohort Study [6] (Abbreviations: HET, heterosexual; IDU, injection drug user; MSM, men who have sex with men; py, person-year)

1.3 Sexual HCV transmission in HIV-infected MSM

In the mid-2000s, outbreaks of acute HCV in HIV-infected MSM were observed in men who reported engaging in various sexual risk practices with mucosal trauma rather than drug-injecting behavior [37, 38]. This drew attention to the sexual transmission of HCV, and particularly to sexual risk behaviors and their respective influences on HCV acquisition.

Since then, sexual transmission has been recognized as an important transmission factor in MSM; however, which behaviors are the main drivers of transmission remain unclear. An ongoing scientific discussion deals with which sexual behavior entails the highest risk and presents the highest-value target. One complicating factor is the high probability of interactions between behaviors [39]. Danta et al. [40] and Chan et al. [38] introduced a biological-behavioral-social framework to facilitate the understanding of the sexual HCV transmission mechanism in MSM.

As HIV-infected MSM are particularly affected by HCV, HIV infection is suspected as a facilitating biological factor increasing their susceptibility to it. However, the existence

such a relationship is the subject of considerable controversy [38, 40-42]. Studies have also shown an increasing incidence of HCV infection in HIV-negative MSM using PrEP. [43, 44]. This suggests that behavioral factors are more influential. Supporting a behavioral link, a United Kingdom (UK) study showed that 40% of HCV infections occurred in PrEP-using HIV-negative MSM active in the same networks as HIV-positive MSM [44].

Furthermore, alongside HIV, other sexual transmitted infections (STIs) are clearly associated because ulcerative lesions disrupt mucosal barriers and can facilitate HCV transmission [39, 40, 42, 45, 46]. This is consistent with SHCS results showing that a previous Syphilis infection could be predictive of HIV/HCV co-infection [47].

Sex-related behavioral factors have been identified as even more important triggers of the HCV epidemic [38, 40]. In particular, practices with risk for mucosal trauma, e.g., unprotected receptive anal intercourse, fisting, use of sex toys, or group sex, were strongly associated with HCV transmission [38, 40, 45, 46, 48, 49].

The impacts of individual risk behaviors are less clear. Whereas Hagan et al. [52] specified certain types of risk factor (e.g., “mucosally traumatic sex while high on methamphetamine”), Schmidt & Bremer [39] argued that this description does not reflect the possible causality of associated factors. Instead, they emphasized the complexity and interactivity of each factor, e.g., methamphetamine use may result in other transmission risks such as sharing of injection equipment or longer duration of sexual contact.

Therefore, instead of promoting condom use alone, Schmidt et al. [48] recommended working with a somewhat broader concept of “blood awareness.” This involves sexual practices which can lead to blood contact and should be equally promoted (e.g., changing blood-contaminated condoms between partners).

Schmidt & Bremer [39]. also emphasized the need to acknowledge sexualized drug use behavior in HCV prevention. In recent years, sexualized drug use (SDU) to enhance sexual experiences has increased in popularity [41, 45, 50-52]. The use of various substances to intensify and/or extend sexual encounters, especially with multiple partners and other high-risk activities is associated with increased potential for anal or rectal trauma [38, 41, 52]. A systematic review investigating HCV transmission in MSM also highlighted injecting drugs, i.e., sharing syringes, as an important transmission route [53].

Recent studies from different countries, especially the UK, indicate higher rates of SDU and associated risk behaviors in HIV-infected MSM. One study in 2248 HIV-infected MSM showed that 51% were using recreational drugs—a practice strongly associated

with condomless anal intercourse [54]. Two other studies in HIV-infected MSM indicated that 29.1%–29.5% of participants engaged in SDU, with 10.1%–16% injecting drugs [55, 56].

Increased SDU not involving injecting is also discussed as an important contributor to HCV transmission in HIV-infected MSM in Switzerland [57]. In one recent SHCS study, the rising prevalence of SDU in 2017, estimated at 13.8% of HIV -infected MSM who used drugs, was significantly associated with an increase of condomless anal intercourse and HCV co-infection [58].

Tied to the increasing popularity of SDU, its interplay with increased sexual risk behavior and/or injecting risks stresses the need for interventions targeting SDU behaviors [8, 39, 59]. While evidence on interventions are scarce, results of a recent cross-sectional study highlighted that MSM engaging in SDU show unmet health needs [60]. Meanwhile, a systematic review identified and described SDU behaviors. Both sets of findings can support the development of further interventions [61].

Behavioral risk factors have to be understood within the context of HIV-infected MSM's changing social environment. Over a number of years, MSM integrated specific prevention strategies to avoid HIV transmission. Two well-known strategies are "serosorting"—sexual decision-making based on HIV-status [40, 62-64]—or the successful implementation of HIV treatment, leading to non-infectious status because of fully-suppressed viremia [65, 66].

Both strategies have successfully reduced HIV transmission but cannot protect against other STIs, including HCV [38, 40, 45]. Within the community of HIV-infected MSM, the broad implementation of effective prevention strategies also influences individual behavior. One important example is sexual risk-taking: when community norms do not support a specific behavior, e.g., condom use, empirical evidence suggests that this can hinder individual uptake of personal preventive measures. However, the converse is also true: a prevalent attitude in favor of condoms can also facilitate their use. However, empirical evidence on how to effectively influence community-level norms via preventive interventions is scarce [67].

Other environmental changes facilitating HCV transmission have also been discussed. Social media networking make sexual meetings quick and uncomplicated [38]. Combined with the ease of international travel, this facilitates HCV transmission to networks across virtually all countries and regions.

To summarize, biological, behavioral and social factors, e.g., sexual practices, SDU, the presence of certain STIs (or their aftermath) and community norms, all play roles in HCV transmission in HIV-infected MSM.

1.4 HCV reinfection

With the expanding application and success of HCV treatment in HIV-infected MSM, the incidence of HCV reinfections is increasing. A meta-analysis of studies conducted in Western Europe between 2002 and 2014 showed an incidence of 7.1/100 py for a first reinfection (after Interferon-based treatment), with this figure rising for further reinfections (18.8/100 py). The same review showed that most reinfections occurred within two years after treatment [68].

Since the introduction of DAA, several countries have re-assessed HCV reinfection in diverse populations. Whereas Spain, Germany and Australia present a low overall reinfection incidence rates (respectively 0.48/100 py, 1.89/100 py, and 0.81/100 py) following DAA treatment, re-infection rates rose considerably in HIV-infected MSM (Spain: 5.93/100 py resp. Germany: 9.02/100 py) [11, 12]. In the Australian study, after 402 people living with HIV received DAA, the only reinfections occurred in MSM [36]. In Germany, 48 of 2298 HCV-cured patients had reinfections within three years after treatment; again, MSM were most affected. Interestingly, MSM who had already been re-infected at least once showed an even higher reinfection incidence rate: 23.93/100 py [12]. And in the Spanish study, all re-infected MSM reported engaging in sexual risk behavior, e.g., unprotected anal intercourse with several partners, sexualized and/or injecting drug use or having had concurrent STIs [11].

These results highlight the impact of ongoing sexual risk behavior on the sustainability of a treatment effect. The same impact is described in two mathematical modelling studies [8, 9], both of which indicate that, in addition to scaling up treatment, a behavioral risk reduction intervention should be offered to MSM to avoid reinfection. Current reviews of HCV studies in this population argue for a combination of medical treatment and sexual risk reduction interventions [37, 69, 70].

To summarize, increased reinfection incidence rates among MSM who engage in high-risk sexual behaviors are strong indicators both that those behaviors facilitate HCV transmission and that HIV-infected MSM remain a key population for enhanced prevention strategies. For the strategy of micro-elimination to succeed, a counselling intervention promoting sexual risk reduction is urgently needed. Such an intervention would need to

target both sexual and drug use risk behaviors that facilitate HCV transmission, and would further need to fit these men's dynamic social environment.

1.5 Evidence-based interventions for sexual risk reduction

Importantly, to our knowledge no evaluated prevention intervention targeting HCV transmission risk behaviors existed before the start of this work in 2015. However, the literature did include several meta-analyses and (systematic) reviews regarding effective evidence-based interventions (EBI) for sexual risk reduction in this population to prevent HIV or STIs in general.

Most previous studies focused on three populations: MSM (7) [71-76]; adolescent heterosexuals and MSM (2) [77, 78]; and people living with HIV (2) [79, 80].

Although the various studies' target MSM populations varied slightly in age or HIV status, they reported two important common results: firstly, which components enhanced intervention effectiveness, and secondly, the difficulty of measuring outcomes. They consider interventions more effective if they are theory-based, match specific needs, integrate skill building, are conducted on an individual level, engage the community in various phases of the research cycle, are delivered by trained professionals and are implemented within multi-professional clinical settings [71-78, 80].

Two reviews also found digital interventions effective for sexual risk reduction in MSM [75, 78]. This is consistent both with a previous meta-analysis and with a 2019 systematic review showing that computer-based interventions are effective in MSM, with some advantages—especially regarding delivery and confidentiality [81, 82].

Regarding the work on behavioral sexual risk reduction interventions in MSM, they also investigated the definition and measurement of outcomes. Their results indicate a field in need of advancement. The assessment of outcome measures was difficult and gave mixed indications. Not surprisingly, most sexual risk reduction interventions focused on multiple behaviors, reflecting the complexity of trying to measure or change sexual behavior. One result was a confusing number of outcome measurements, e.g., condom use during either intercourse or other risk-related activities, number of sex partners, sexual abstinence, knowledge of HIV, self-efficacy, attitudes regarding safer sex, etc. Such a proliferation of study outcomes limits inter-study comparison [72-76, 78-80], as does inconstancy between outcome definitions. As noted in the review by Flowers et al. [75], for example, some studies simply measured unprotected anal intercourse over the previous 6 months, whereas others asked more complex questions about unprotected anal intercourse with non-steady partners over the previous 90 days.

Ultimately, the common problem is one of researchers defining appropriate outcome measures. This is consistent with Protogerou et al. [77], who identified a major problem even in the definition of “sexual-risk taking”. They argued that it functions as an umbrella term, denoting numerous behaviors, to which equally numerous measurements can be applied. This could further explain the lack of valid and reliable instruments to measure it.

In sum, reports on sexual risk reduction programs provide evidence on how an intervention looked, which behavior change methods were tried and, of those, which worked, and which elements made the intervention effective. They tend to be less clear regarding which behaviors should be targeted and which outcome measures and instruments are best used to evaluate effectiveness.

1.6 The Swiss HCVree Trial

The Swiss HCVree Trial was launched in 2015 within the framework of the Swiss HIV Cohort Study (SHCS), a representative cohort of HIV-infected people living in Switzerland [83]. Its overall aim was to test micro-elimination of HCV in the population of MSM living with HIV via a combination of DAA treatment and behavioral counselling. From study start until 2017, because of the extremely high cost of DAA, the mandatory Swiss health insurance program only reimbursed the medication costs for patients with advanced liver fibrosis. However, participants received treatment for no charge [84].

More concretely, the Swiss HCVree Trial was planned as a phase III, multi-center, open-label trial. It worked in three phases: In phase A, all HIV-diagnosed MSM participating in the SHCS were systematically screened for HCV co-infection. This indicated 177 (4.8%) with replicating HCV [84]. In phase B, 122 (3.3%) received DAA for free as part of the study. Of these, 121 achieved sustained virological response.

Apart from medical treatment, all of these men received written information about HCV reinfection risk [85]. The trial also integrated a newly developed counselling intervention for voluntary participation. In order to save resources, only men whose situations were considered high-risk were invited.

At that time, the best-known risk behavior was condomless sex, e.g. a recent investigation in the SHCS had identified an increasing incidence of condomless sex with non-steady partners (nsCAI) in HIV-infected MSM (approx. 15% in 2013) [86]. In HIV/HCV co-infected MSM, the regularly assessed SHCS data on condomless anal intercourse with non-steady partners showed that almost half of the study participants would qualify for the behavioral intervention group if this behavior was taken as the inclusion criterion.

In the final phase—phase C, all HIV-infected MSM in the SHCS were re-tested.

Because no behavioral intervention was available to reduce HCV reinfections by targeting sexual risk reduction in HIV/HCV-infected MSM, we had to develop one. Further, the intervention was to be implemented in the Swiss HCVree Trial, which was aimed at micro-elimination—a strategy for which a control group design was impossible. Therefore, evaluation of the impact of the behavioral intervention was more challenging.

This added complexity reflects the starting point of this thesis, which dealt with the development and evaluation of the behavioral counselling intervention within the Swiss HCVree Trial. The following two chapters introduce the theoretical approach and present arguments in favor of the chosen methodology.

1.7 Development and evaluation of a complex intervention

Structuring a study around an existing research framework helps focus and systematize it in a way that increases understanding [87]. This helps ensure comparability of results and avoids significant methodological gaps or pitfalls. Therefore, the development and evaluation of our behavioral counselling intervention was guided by the MRC *framework for complex interventions in health* [88, 89]. With it, the MRC supports researchers by providing a broad structure that divides the research process into four cyclical phases, each of which includes questions formulated to help researchers choose appropriate methods [88].

The phases are: 1) systematic intervention development based on the best available evidence and theoretical foundations; 2) feasibility- and pilot-testing a new intervention; 3) evaluating both outcomes and processes to better understand the intervention's implementation, mechanism(s) of impact and contextual factors; and 4) implementation of the intervention into daily practice [88]. As fig. 2 illustrates, not only the entire process but all parts of it are designed to be repeated as often as necessary.

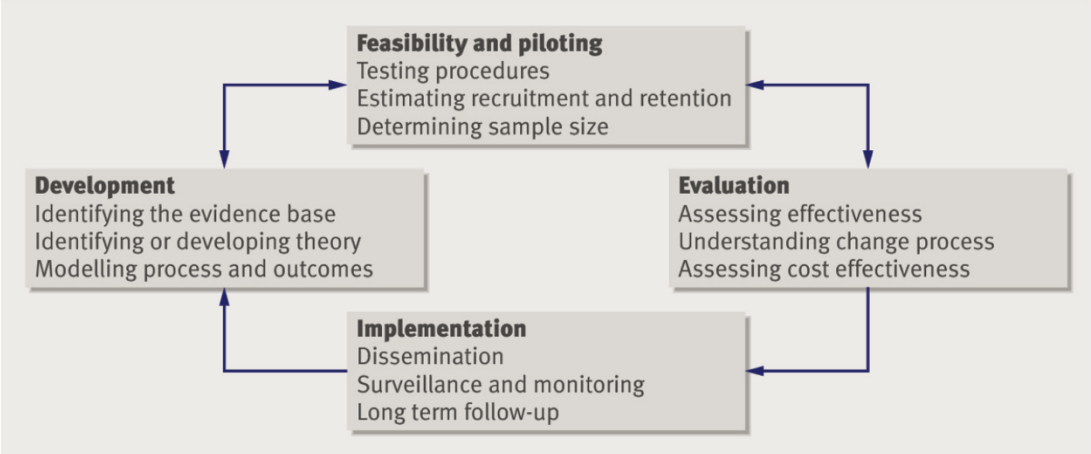

Figure 2: The four phases from the MRC framework [88]

Within the MRC framework, an intervention is classified as complex when it contains a number of distinguishable—though often difficult to measure—interactive behaviors. Further, complexity also increases with the number and variability of an intervention's outcomes and in the degree of its flexibility and tailorability [88].

The behavioral counselling intervention targeting sexual risk reduction to be developed for use in the Swiss HCVree Trial can be considered a complex intervention: It will target several distinct but interactive behaviors—indicating needs both for individual tailorability and for a separate outcome measure for each. And in the absence of a clear definition of the concept of "sexual-risk taking," the matter of which measurements should be taken and how raises the question of whether available instruments are sufficiently valid and reliable [77].

This thesis involved the first two phases of the MRC framework, i.e., intervention development, followed by feasibility testing.

Development of a complex intervention

Recognizing that a complex intervention's success and sustainability are both rooted in its development [90], the MRC framework's development phase emphasizes the importance of a systematic theory- and evidence-based approach [91]. This involves the identification of reliable evidence, e.g., in systematic literature reviews or expert rounds, that supports an understanding first of the health problem and second of what an intervention is intended to change.

Further, explaining how an intervention will work, including a sound definition of the activities and processes necessary for later evaluation, requires a firm theoretical basis

[88]. To date, the framework has focused on testing new interventions via a randomized controlled trial (RCT) design; but this is not without criticism. For example, RCT effect-size measurement provides no information as to an intervention's interactions with its context [92].

In 2018, the MRC itself announced that they are currently updating their guidance, with the aim of integrating other methods [93]. In public health, the MRC guidance, which currently focuses strongly on control group design, is actually a problem in itself; and experience shows that the medial time that elapses between a complex intervention's publication and its implementation into clinical practice—if it is not simply forgotten—is approximately 1.5 decades [94]. To achieve urgent public health aims such as micro-elimination of HCV in HIV-infected MSM, prevention interventions that combine medical treatment with behavioral change intervention demand implementation not in decades or even years but in months, and have to be available to all members of the target population.

Therefore, in line with the spirit of the MRC framework, increasingly innovative approaches to intervention development have emerged. One opportunity is to work with the concept of scaling-out—a strategy to implement an EBI in a closely-related clinical field, in a new population and/or with a different delivery mode [95]. In contrast to the better-known concept of scaling-up, scaling-out emphasizes the further development and adaptation of an EBI (to meet context- or setting specific needs) rather than simply adopting it under real-world conditions [96]. However, in supporting translation of an EBI into practice, both strategies follow the aim of improving health outcomes while conserving resources [95, 96]. As we aimed to develop an appropriate intervention faster by building up on evidence already tested for effectiveness in an RCT, we chose to follow this strategy.

Scaling-out implies adaptation, i.e., change or modification by a user [97] of an existing intervention and/or implementation strategies to improve its fit to a new context while maintaining effectiveness [95]. Improving fit is the most popular reason for planned adaptations [98, 99]. Chambers & Norton [100] argue that adaptation is both an essential step to translate any EBI into practice and an opportunity to constantly evolve them. Aarons et al. [95] see adaptation as inevitable to fit an intervention to a new context while remaining its effectiveness.

In the context of HIV prevention, adaptation is a well-known methodology to make EBIs accessible to the community faster while conserving resources [101] but not reducing their effectiveness [102, 103].

Guidance regarding which framework to choose is also available. Escoffrey et al. [104], for example, identified and reviewed 13 available process frameworks. All use a step-by-step approach, show agreement for many steps but differ in the degree of specification.

In our research, we aimed to improve an EBI focusing on HIV prevention to an HCV prevention context—a type II scale-out. We selected an EBI effective for sexual risk reduction (to avoid HIV/STI transmission) in HIV-infected MSM [105, 106], aiming to adapt it to prevent HCV reinfection in HIV/HCV co-infected MSM.

Because the MRC framework only provides a rough structure, we chose a related framework—Intervention Mapping (IM) Adapt —to guide our adaptation process. Its advantage was that it provides more detailed guidance, follows six steps, and focuses clearly on adaptation [103]. Using this systematic approach, we developed the *HCVree and me* intervention, which was afterwards integrated into the open-label Swiss HCVree Trial.

Evaluation of feasibility testing

As the next phase, the MRC framework suggests testing the newly developed intervention in a pilot or feasibility study. This phase offers an opportunity both to learn more about the intervention and its effects and to better understand the processes before a full trial [88, 90]. The MRC also emphasize that this is a good point in the process to address various feasibility criteria, e.g., participants' and health care professionals' perceptions of the intervention's relevance, or to identify barriers to implementation [89, 90, 107, 108]. In line with the MRC framework, many others stressed the importance of evaluation to resolve uncertainties regarding the intervention as well as to guide further improvements to it [109-112].

However, at the moment, a gap remains in the literature about how to evaluate an adapted intervention [113]. In of the absence of specific guidance, we used the Swiss HCVree Trial as a feasibility test to assess questions concerning clinical, methodological and procedural evaluation [90].

Our work was based mainly on the extended 2015 MRC guidance document. In this update, the MRC emphasizes the importance of the process evaluation, which the writers rank alongside that of outcome evaluation. They also emphasize the importance of additional evaluation on implementation, intervention's causal mechanism and influencing contextual factors, especially for situations in which no RCT is possible [89].

Knowing that the Swiss HCVree Trial's pre-post design would hinder a meaningful outcome evaluation, we expanded to process evaluation to maximize this study's impact. In a context of increasing demand for parallel behavioral and biomedical interventions, the

results are essential both for further development and to indicate intervention's scalability [96].

Pursuing a number of evaluation aims promoted our learning in each of those areas. Feeley & Cosette [111, p.167] formulated two main research questions for this phase: "Can the intervention be provided as planned?"; and "Is the intervention acceptable for participants?" Problematically, both questions can target several intervention features and need to be further specified. Only once they are fully clear will it become possible to select the research method that yields the most meaningful results.

As Moore et al. [89] recommended, we first defined evaluation questions and aims, then choose an appropriate method. They also emphasized the use of a mixed-method design. Whereas qualitative approaches are essential to capture causal impact mechanisms, interactions and influencing contexts [92, 114, 115], quantitative approaches are more useful to investigate not only outcome effects, but also implementation fidelity.

Because we were testing what was, to our knowledge, one of the first HCV behavioral interventions, we were especially interested in evaluating its causal mechanism. For the purposes of the MRC framework, this involves how participants respond to an intervention and how it produced an intended change [89]. To explore it, we analyzed qualitative data on participants' responses to the intervention and on participant's goal-setting and quantitative data on self-reported behaviors.

Together, the results supported our understanding of how our behavioral risk counselling worked and what impact it had on behavioral changes. As we were also interested in evaluating implementation processes, we assessed how closely the nurse counsellors adhered to the defined procedures (content, dose, timeliness and coverage). Additionally, we evaluated the intervention's reach by asking whether the right MSM received the intervention.

1.8 Research gap and rationale for this dissertation

The provision of broad HCV treatment shows limited success, especially in defined subpopulations who engage in ongoing transmission risk-taking. This situation calls for a comprehensive prevention strategy which includes a behavioral counselling intervention. The Swiss HCVree Trial pursued such a strategy; however, in 2015, no behavioral intervention was yet available for HIV-infected MSM.

To address this urgent demand, the research team systematically developed an appropriate intervention and evaluated its feasibility. By reflecting the related processes, this

dissertation will contribute to the understanding of the prevention of HCV reinfection in HIV-infected MSM. It will also offer guidance on how to enhance the efficiency of work on the concept of scaling-out. Equally significantly, it illustrates how maintaining the fit of a behavioral counselling intervention targeting such a heterogeneous group in such a dynamic sexual environment requires constant adaptation.

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Chapter 2. Aims

The overall aim of this thesis was to strengthen a comprehensive behavioral prevention strategy to improve HCV micro-elimination. This involved the development of an HCV specific sexual risk reduction intervention by adapting an evidence-based HIV sexual risk reduction intervention, followed by feasibility testing of the new version within the framework of the Swiss HCVree Trial.
The thesis is comprised of four distinct phases, each of which deals with a specific aim:

1) Describing the systematic adaptation process to improve the fit of an evidence-based intervention to an HCV prevention context, followed by a clear description of the new *HCVree and me* intervention **(chapter 3)**.
2) Describing the sensitivity/specificity of the selection criteria chosen for the behavioral counselling intervention in identifying men who engaged in HCV relevant risk behaviors other than condomless anal intercourse with non-steady partners and, therefore, who might also benefit from this behavioral intervention **(chapter 4)**.
3) Gaining an understanding of the intervention program's meaning to its participants regarding both their sexuality and their risk behaviors **(chapter 5)**.
4) Validating the hypothesis that the three qualitatively generated sense-making work groups also differed in the content of sexual risk reduction goal-setting and behavior change post-intervention **(chapter 6)**.

Chapter 3. "Scaling-out" an effective sexual risk reduction intervention to prevent hepatitis C reinfection in HIV-diagnosed men-who-have-sex-with-men: Systematic adaptation and intervention description

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3.1 Abstract

The World Health Organization's hepatitis C virus (HCV) elimination goals demand innovative preventive approaches. Because HCV reinfection is more frequent in HIV-diagnosed men-who-have-sex-with-men (MSM) than in other groups, a combined medical/behavioral intervention might be beneficial.

In 2016, to evaluate the feasibility of a comprehensive prevention program targeting HIV-diagnosed MSM in a representative national cohort, a treat-and-counsel strategy was integrated into the Swiss HCVree Trial. This report describes how we scaled-out, (i.e., adapted and implemented) an evidence-based intervention for use in a closely related clinical field. Beginning with an intervention originally aimed at sexual HIV transmission risk reduction, after conducting a contextual analysis, we used the six-step Intervention Mapping Adapt framework as a guide to repurpose it to one tailorable for use against HCV-reinfection in formerly HIV/HCV co-infected MSM.

This report describes our adaptation process results step-by-step, followed by a presentation of the final *HCVree and me* intervention, which now targets HCV risk reduction by improving self-regulation of risks associated with sexual behaviors including sexualized drug use. Scaling-out an existing intervention instead of developing a new one allowed us to build upon existing evidence despite the scarce knowledge in this field, while possibly shortening the process of research translation.

Clinical Trial Number: NCT02785666, 30.05.2016

Keywords

Intervention adaptation, scaling-out, HIV, Hepatitis C Virus, MSM, sexual risk reduction

3.2 Background

Men-who-have-sex-with-men (MSM) living with HIV have shown elevated rates of hepatitis C virus (HCV) infections since the mid-2000's [1, 2]. Among MSM, increased incidence and prevalence of HIV/HCV co-infection are associated with inconsistent condom use and sexualized drug use (SDU) [3-5]. Further, sexual and drug use risky behavior is an important reason for this group's remarkably high reinfection rates after successful HCV treatment (10-15/100 persons per year) indicating HIV-diagnosed MSM as a key group for additional prevention efforts [1].

The World Health Organization's (WHO) global HCV elimination goals include an 80% reduction in new HCV infections and a mortality reduction of 65% by 2030 ([6], based on the availability of well-tolerated effective direct-acting antivirals (DAA) with cure rates of over 95% and reduced liver-related morbidity and mortality [7]. To reach these goals, micro-elimination, i.e., targeting of very specific populations, is now discussed as a viable strategy [8]. In this regard, HIV-diagnosed MSM are a well-defined target group with a chance to achieve HCV micro-elimination because they constitute a rather closed population (e.g., 6300 HIV-diagnosed MSM living in Switzerland [9]).

In the absence of a vaccine, micro-elimination depends on two prevention strategies: first, increased HCV screening followed by treatment uptake; and second, behavioral change to reduce sex and drug-related HCV infection/reinfection risks. This is supported by modeling studies from the United Kingdom [10] and from the Swiss HIV Cohort Study (SHCS) [11]. However, both showed that HCV micro-elimination goals cannot be reached through increased treatment uptake alone but require reduction in risk behavior. Therefore, the combination of HCV treatment and behavioral intervention is vitally relevant to public health.

Based on increased prevalence and incidence of HIV/HCV co-infection in MSM living in Switzerland [2], the Swiss HCVree Trial was initiated in 2016 using a micro-elimination approach. The trial worked in three phases: 1) systematic HCV screening of all MSM enrolled in the SHCS; 2) provision of free HCV treatment to HIV/HCV co-infected MSM (in Switzerland, until October 2017, high-drug pricing DAA were only reimbursed for patients with advanced liver disease); and 3) a behavioral sexual risk reduction intervention for HIV/HCV co-infected MSM to reduce HCV transmission risks. While the Swiss HCVree Trial's efficacy and safety results have been reported elsewhere [12], we focus here on the systematic development and description of the behavioral intervention.

When the study started in 2016, a literature review and expert consultations could not identify any published HCV-specific behavioral risk reduction interventions for MSM.

Rather than starting from scratch, we chose to build upon existing evidence by employing the concept of scaling-out, i.e., the strategy of implementing an evidence-based intervention (EBI) in a closely related clinical field, in a new population and/or with a different delivery mode—not to be confused with the better-known concept of scaling-up, which involves delivering an EBI to more people and places.

Scaling-out implies adaption of an intervention and/or implementation strategies to improve the intervention's fit to a new context while maintaining effectiveness. This warrants a thoughtful and systematic adaptation process to meet the requirements of the new field while identifying and maintaining core elements for effectiveness. Currently, three types of scaling-out are described: type I, adaptation for a different delivery mode; type II, adaption to a different population; and type III, adaption to both a different delivery mode and a different population [13].

For the Swiss HCVree Trial intervention, sound evidence from prevention programs targeting sexual risk reduction in people living with HIV [14] allowed a type II scale-out, i.e., targeting a slightly different population (e.g., HIV/HCV co-infected MSM) but the same delivery mode [13]. This methodological report's purpose is to describe how we followed the concept of scaling-out by adapting an EBI originally aimed at sexual risk reduction to prevent HIV transmission in MSM to one aimed at preventing HCV reinfection in formerly HIV/HCV co-infected MSM.

Therefore, the aims of this work are 1) to describe the methodology used for systematic intervention adaptation, presenting the process results step-by-step; and (2) to introduce the resulting *HCVree and me* intervention. Both steps are crucial to the dissemination and scaling-out of one of the first behavioral interventions designed to prevent HCV reinfection in HIV-diagnosed MSM.

3.3 Methods

Our systematic scale-out process was guided by the six-step Intervention Mapping Adapt (IM Adapt) framework and a contextual analysis. IM Adapt is an empirically validated framework with an explicit focus on decision-making by examining a selected EBI in relation to a new target setting [15]. To further support this decision-making technique, the entire adaptation process was based on a contextual analysis informed by the multi-level framework described by Chaudoir et al. [16]. This framework was developed to promote the implementation of EBIs into daily practice and to define implementation outcomes. We used it as a practical tool to cover all levels of intervention adaptation. This allowed us to account for context, i.e., a "complex adaptive system that forms the dynamic

environment(s) in which implementation processes are situated" and therefore to include stakeholders at various levels from the beginning in the process [17, 18].

For our contextual analysis we conducted individual and/or small group interviews with structural-, organizational-, provider- and patient-level stakeholders: members of the SHCS and/or of the Swiss Hepatitis Strategy (a national expert group aiming to coordinate the activities of many parties involved in hepatitis research, prevention and treatment) (n=2) [19]); heads of SHCS clinical centers (n=4); from representatives of patient organizations (n=2); from HIV/HCV nurses and physicians (n=6); and from HIV/HCV co-infected MSM (n=4). Using knowledge-mapping techniques, data analyses focused on themes relevant to intervention content and implementation [20].

Below we describe the methods used along the six steps of the IM Adapt framework, including relevant information obtained from our contextual analysis.

Step 1: Needs Assessment

This step's purpose was first to increase our understanding of risk behaviors most relevant to HIV/HCV co-infection in MSM. Second, it allowed us to examine this group's needs regarding sexual health. Therefore, we conducted a systematic literature review and meta-analysis regarding sexual and non-sexual behaviors and associated risk factors affecting HCV transmission in HIV-diagnosed MSM. Further, we reviewed both qualitative and quantitative descriptive research to establish a literature map of this population's needs. From the contextual analysis, we integrated patients' and clinicians' perspectives on risk reduction and sexual health needs. Findings were summarized in a table to inform the development of a preliminary logic model for change.

Step 2: Assessment of the intervention's basic fit

This step's purpose was to identify an EBI with the potential for type II scaling-out. We reviewed the literature on EBIs from the field of HIV-related sexual risk reduction for MSM and evaluated the program's basic fit, focusing on three criteria suggested by Bartholomew et al. [15]: 1) fit with the actual health problem; and 2) fit with the at-risk group; and 3) fit with that group's organizational capacity (for which we used setting information collected from clinicians in the contextual analysis).

Step 3: Assessment of detailed fit and planning of adaptations

This step's purpose was to assess the detailed fit and planning of adaptations. To do so, the research team contacted and worked with the selected EBI's developers [21]. The research team's primary investigator provided access to their knowledge, study materials and the computer-assisted tool they developed for their randomized controlled trial

(RCT). Following a point-by-point procedure, we compared the fits of the EBI components with those of our three preliminary logic models of change components: 1) behavior and environment based on performance objectives (POs); 2) determinants and change methods; and 3) delivery and implementation [15]. This step's product was a final logic model of changes.

Step 4: Making Adaptations

Adaptation suggestions were then examined in light of original documents and study materials. The research team and two community members made the final decisions about adaptations.

Step 5: Planning Implementation

Based on the contextual assessment in step 1, the research team collaborated with the stakeholders to define and establish a plan to implement the intervention within the Swiss HCVree Trial setting.

Step 6: Planning evaluation

The final step consisted of planning the evaluation of the adapted intervention. This included defining outcomes and measures essential to the final product (i.e., the *HCVree and me* intervention). The final intervention was reported in the template for intervention description and replication (TIDieR) checklist to improve the intervention's further use [22].

3.4 Results

In this section we first present the process outcomes for each step of the intervention adaptation, followed by a description of the new *HCVree and me* intervention.

Step 1: Needs assessment

Key findings from the literature review and multi-level contextual analysis were summarized in table 1. The results showed that sexual risk behaviors of MSM with HIV linked to HCV transmission are associated with blood and mucosal trauma [23, 24]. SDU facilitates higher sexual risk taking [25] and the drug use can be unsafe [4, 23, 26]. Additionally changed community norms regarding sexual risk-taking [27] with decreased condom use [28], and problems of HCV disclosure [29] have been described. Findings from the contextual analysis matched the results from literature review but highlighted the influence of the changed context. HIV/HCV co-infected MSM described impressively

observed changes in individual sexual behavior but also within their community. The clinicians emphasized the importance of SDU in HCV prevention.

Table 1 Findings summarized from literature review and contextual analysis

	Literature review	Contextual analysis	
		Patient-level	**Provider-& structural level**
Sexual and non-sexual behaviors associated with HCV transmission risk	Unsafe sex practices involving mucosal trauma and blood exposure (e.g. unprotected anal intercourse with multiple partners, fisting, use of sex toys); e.g., [23, 24]		MSM with an HIV/HCV co-infection might differ from MSM with HIV monoinfection in terms of their sexual risk behavior, in particular SDU
	Unsafe SDU (e.g. sharing needles, snorting tubes, prolonged sexual encounter) SDU facilitates higher sexual risk taking (e.g. prolonged sexual encounter, multiple partners), e.g., [4, 23, 25, 26]	The feeling of sliding unprepared into SDU practices	Other topics were related to the content of a counselling intervention e.g. to not only focus on condom use but to promote other risk reduction strategies. Difficulties to decide what outcomes should be measured
	Impact of contextual changes (e.g., the Swiss Statement 2008 on condom use [52]); e.g. [28] Changed community norms; e.g., [27]	Feeling invulnerable because of HIV	All has changed since the Swiss Statement, less MSM use condoms
	HCV disclosure is difficult in because of feared stigma and rejection; e.g., [29]	HCV disclosure does not work like HIV disclosure Difficulty to find a non-stigmatizing healthcare provider	Physicians feared recruitment problems because they described MSM are emotionally vulnerable or stressed by additional effort the behavioral intervention would mean.
Organizational capacity			No personnel resources for counseling available but willingness to recruit Agreed for the provision of space and infrastructure Nurses show interest in being counselors

Step 2: Assessment of the intervention's basic fit

We identified effective interventions with potential for type II scaling-out. The best match was the "Computer-assisted Intervention for Safer Sex" (*CISS*), developed and tested in HIV-diagnosed MSM in a European RCT conducted in seven treatment centers. At three months' follow-up, compared to control participants, the intervention group (n=55) showed a significantly higher level of condom use at last intercourse (OR 3.83; p=0.03) [30]. Additionally, results of the *CISS* process evaluation indicated feasibility in various European care settings and high satisfaction among both participants and providers (>80%) [21].

We identified a good match both with the health problem and with the at-risk group: the original EBI focused on reducing HIV transmission and/or STI co-infection in HIV-infected MSM and focused on risk behaviors similar to those we intended to target [21]. Additionally, our target group's organizational capacity matched that of their *CISS* counterparts well: the *CISS* intervention trial was conducted in a setting similar to that planned for *HCVree and me* and with access to similar resources (e.g., HIV outpatient clinics; health care providers with training as interventionists).

Step 3: Assessment of detailed fit and planning of adaptations

As recommended, we first compared **behavior and environmental** fit on performance objectives (POs) to refine the preliminary logic model of change. We judged the CISS POs as still relevant but in need of expansion. Partly because *CISS* was developed before the Swiss Statement of 2008, its main focus—condom use—seemed too narrow to prevent HCV transmission in 2017 [31].

More urgently, the adapted intervention would need to address certain sexual practices, especially those entailing either risks of rectal trauma/bleeding [24] or those involved in combining drug use with sex [10]. Therefore, we planned to refine existing POs to allow for content adaptations that both focused on HCV and facilitated integration of our new POs and behavioral outcomes, e.g., safer SDU and enhanced communication (see table 2).

Table 2 Logic Model of Change

Individual determinants	**Performance objectives (POs)**	**Behavioral outcomes**	**Health outcome**
• Self-efficacy • Skills • Knowledge • Risk perception • Normative beliefs • Outcome expectations • Perceived susceptibility • Perceived barriers •	• Make accurate sexual risk assessment *for HCV transmission* • Adopt 'less risky' sexual practices *(avoidance of traumatic practices)* • Plan ahead to adopt safer sex behaviors • Negotiate safer sex with *non-steady partners* • Plan ahead for condom use *with non-steady partners* • Negotiate condom use *with non-steady partner* • Use condoms correctly and consistently • Reduce number of sexual partners • *Plan ahead to adopt safer drug use* • *Use drugs safely* • Disclose HIV to sexual partners • *Disclose HCV to sexual partners* • *Plan to discuss topics with HCPs*	Decreased sexual risk behavior *with less exposure to blood and mucosal trauma* • Protected sexual practices *when risking rectal traumas* • Increased condom use with non-steady partners • *Safe sexualized drug use* • Healthy dating with steady or casual sexual partners • *Enhanced disclosure of HCV with sexual partners* • *Enhanced communication about sexual risk behavior between MSM and HCPs*	*Reduced incidence of HCV reinfection*

In italics, adaptations needed on CISS

Determinants and change methods from the original intervention were judged as key for the change process and therefore left unchanged (see table 2). Importantly, the *CISS* intervention was also based on neurocognitive evidence that, as a basis for sexual decision-making, logical reasoning was overrated; in its place, automated, intuitive behavior was more likely [32, 33]. Therefore, visual materials were chosen for their power to evoke emotions and highlight such implicit processes. This allowed clearer insights into the types of dissonant behaviors upon which counseling can focus. We chose to expand the original visual materials content-wise across a range of HCV-specific topics and to continue with motivational interviewing techniques, as these increase participants' readiness to communicate their thoughts and impressions [21].

Delivery and initial implementation of the original *CISS* intervention was provided by trained healthcare providers working in the clinical centers. The contextual analysis showed no personnel resources in the clinics but nurses with HIV/HCV care expertise with serious interest in assisting. We decided to recruit and train these nurses to provide the intervention sessions for participants in 1-2 centers following the medical treatment consultation segment of the Swiss HCVree Trial.

CISS included three individual counseling sessions, supported by interactive video/audio materials [21]. Six months post-intervention, *CISS* showed a diminishing effect; therefore, to extend the intervention effect, we planned to integrate a short booster session, evaluating effects of the individualized change plan after the third *CISS* session. The *CISS* materials were available in English with subtitles in German and French. The eHealth tool required minor linguistic adaptations.

Step 4: Making adaptations

Adaptation suggestions and ideas, particularly from step 3, were discussed in the team until consensus was reached. We then defined what their practical realization should include. We agreed, for example, that new HCV content should be integrated via six additional video clips. Based on original interview quotes, short 2- to 3-minute video scripts were written by one researcher, reviewed by community members and filmed using actors. Video clips were followed by information tools (e.g., texts, lists of frequently-asked questions). Remaining *CISS* material was translated into French and German and integrated into a password-accessible eHealth website (www.hcvree.ch). Additionally, we recruited community members to provide pre-trial feedback on the acceptability and feasibility of the new intervention, which was now named *HCVree and me*.

Step 5: Planning implementation

After the adaptation phase, the intervention was implemented within the framework of the Swiss HCVree Trial—or, more concretely, in parallel with medical consultations during HCV treatment. All participants received written information on HCV transmission risks (e.g., blood exposure, unsafe sexual practices, unsafe drug use) [12]. The one inclusion criterion for the additional behavioral intervention was reporting inconsistent condom use with non-steady partners in the year prior to study inclusion [34].

At the study initiation visit, via one-hour presentations, we gave healthcare providers from seven centers detailed information on recruitment procedures and the structure of the behavioral intervention. Five nurses were given three hours' training in person-centered and motivational communication techniques, plus two hours to familiarize themselves with the eHealth-based intervention procedures. A research assistant coordinated interventionists' and patients' schedules for all participating centers. Throughout the trial, the research team supported the interventionists in discussing and reflecting on their most challenging cases.

Step 6 Planning evaluation

Given the setting of the clinical trial testing micro-elimination and the difficulty of defining an adequate control group, the research team decided to perform a single-arm feasibility study with a pre-post study design. As this design would hinder a meaningful outcome evaluation, we expanded to process evaluation to maximize its impact [35]. We were interested in three specific evaluation aims: 1) to assess recruitment and participation rates, while noting how the actual intervention implementation compared to the pre-defined procedures; 2) to qualitatively explore participants' responses to the intervention; and 3) to quantitatively analyze pre-post behavioral outcomes.

The *HCVree and me* intervention

The new *HCVree and me* intervention is adapted to target HCV instead of HIV risk reduction by improving self-regulation to risks associated with sexual risk behavior and sexualized drug use (see table 3). As a theory-based intervention, it follows an adapted version of the information-motivation-behavioral (IMB) skills model [36, 37], social cognitive theories (SCT) [38], and the transtheoretical model (TTM) [39], along with theoretical aspects of cognitive neurosciences and motivational interviewing techniques [40]. An interactive web-based tool supports the tailoring of content to patient needs, as well as reflection on sexual behavior-associated risks and action planning.

For our trial, interventionists were nurses with expertise in caring for patients with HCV and/or HIV. The intervention was applied in four one-to-one sessions. Driven largely by the patients' preferences, these differed in content and aims.

The first focused on exploring the participant's emotions and values regarding his own sexual and drug use behaviors. Participants could choose video clips according to their particular interests and needs. Thirteen videos were available on five topics: 1) Love & relationships; 2) Thinking & emotions; 3) Sex & desire; 4) Stimulating substances; and 5) Sex & health. Each clip was followed by a discussion on the participant's emotional response.

The second session focused on perceived benefits and disadvantages of the participant's current sexual behavior and possible behavior change. This was also supported and tailored via video clips, but with a greater focus on information and reflection of the participant's individual situation (e.g., in what situations during sex do I risk injury/bleeding?).

The focus of the third session was individual goal-setting: each participant formulated individual goals for behavioral change congruent with his preferences and confidence to achieve those goals. And in the fourth, their implementation was discussed, reflected on, and reinforced.

Intervention sessions were scheduled in the HIV outpatient clinic within the frame of the Swiss HCVree Trial visits, following HCV treatment appointments at treatment weeks 4, 6, 8 and 12, with an allowed range of ± 14 days. The first three sessions lasted 45–60 minutes each; the fourth was a 20–30-minute booster session to reinforce the effects of the first three. Between sessions, participants could continue to use the interactive web-based tool independently.

Table 3 Intervention *HCVree and me*

No	Focus	Theory-base	Delivery	Procedure	Format	Content	Time and Dose
1	**Who am I?** Meaning of sexual and drug use behaviors for clients to understand "why they do what they do"	Neurocognitive sciences (hot and cold thinking) IMB: Focus on motivation	Individual eHealth assisted counseling using MI techniques 45-60 minutes	Introduction Exploration of meanings related to sex, drug use and associated problems Watching one or two selected videos Discussion of reactions to the video(s) Summary and outlook	Case-vignettes presented in video clips, Emotional stories presenting one problem with a solution	5 overriding topics 1) Love & Relationship 2) Thinking & Emotions 3) Sex & Lust 4) Stimulating substances 5) Sex & Health	Treatment week 4 +/- 14 days Before or after medical appointment at the HIV outpatient clinic 45-60 minutes
2	**Working through** Developing solutions for identified problems	IMB Focus on motivation, information, decisional balance TTM SCT for modeling	Individual eHealth assisted counseling using MI techniques 45-60 minutes	Reflection on first session Exploration of different approaches to making safer sex simpler in participants' individual situations Information provision Summary	Interactive information and reflection material	4 overriding topics 1) Talking about HCV/HIV 2) Thinking & Emotions 3) Blood awareness/safer sex 4) Sex, drugs and risks	Treatment week 6 +/- 14 days Additional visit without medical appointment at the HIV outpatient clinic 45-60 minutes
3	**Making a plan** Working on strategies for goal setting and change	IMB Focus on skills Goal-setting TTM SCT for self-efficacy	Using MI techniques 45-60 minutes	Reflection on second session Discussion of smart goals Exploration of skills and self-efficacy Writing a plan	Discussion Goal-setting material	Making an individual plan	Treatment week 8 +/- 14 days Before or after medical appointment at the HIV outpatient clinic 45-60 minutes
4	**Evaluating my plan** Reflection on goals and implementation	IMB Focus on skills TTM Self-efficacy	Using MI techniques 30 minutes	Exploration of goal-setting and experiences with implementation Reinforcement and outlook	Discussion		Treatment week 12 +/- 14 days Before or after medical appointment at the HIV outpatient clinic 20-30 minutes

IMB, Information-Motivation-Behavioral skills model; SCT, social cognitive theories; TTM, transtheoretical model; MI, motivational interviewing techniques

3.5 Discussion

This paper presents a systematic process of adapting an intervention originally aimed at preventing HIV transmission by HIV-diagnosed MSM for use in the context of MSM living with both HIV and HCV. In a step-by-step approach resulting in a type II scaled-out intervention, major adaptations were performed.

This process was additionally based on a contextual analysis, which was vital for decision-making. We expanded the focus from condom use to include a range of sexual risk behaviors important in the context of HCV transmission. We also adapted the implementation strategy and evaluation plan because the intervention's use in a micro-elimination trial precluded a control group design.

Since the mid-2000s, HCV incidence has been increasing among HIV-diagnosed MSM, indicating an urgent need for behavioral HCV prevention interventions, especially to avoid reinfection after successful treatment [1, 11]. To our knowledge, no behavioral intervention targeting this specific issue has previously been developed.

However, rather than developing a behavioral intervention from scratch, we opted to scale-out an existing EBI, building on sound evidence arising from prevention interventions in HIV-diagnosed MSM. Scaling-out includes adaptations to fit the original intervention to a new context [13]. Castro & Yasui [41] underscored the importance of adaptation as a problem-solving method—the problem being to fit interventions to new environments while maintaining the original EBI's theoretical foundations.

Bartholomew et al. [15] further emphasized the importance of a systematic approach to identifying and retaining elements essential to the original EBI's effectiveness. Therefore, we used the IM Adapt framework to guide the adaptation regarding acceptability, fit and effectiveness [42, 43]. Step-by-step guidelines [44, 45] also simplified the adaptation reporting process, thereby facilitating both the intervention's reproducibility and later evaluations of its effectiveness.

In addition to the IM Adapt Framework, a contextual analysis [16] supported our efforts to account for the context's dynamic nature [17, 18]. This was necessary because the CISS intervention's development started several years before and was tested until 2013 [21]. When we began the research that led to this scaling-out, important contextual changes, e.g., the broad implementation of the Swiss Statement, had influenced sexual behaviors in HIV-diagnosed MSM. Consequently, it was clear that to use this EBI in our context we would need to adapt it, adjusting its structure to fit the most significant changes via a type II scale-out. This also follows the recommendation of Chambers et

al. [46], who approached adaptations as an opportunity to further develop existing evidence, especially through the integration of current knowledge, and to account for dynamic contexts.

Adhering to the IM Adapt recommendations, conducting a thorough contextual analysis and pursuing a highly participatory strategy all strengthened the adaptation process considerably. In particular, early stakeholder involvement, including mutual learning, was extremely valuable, as was proactive definition and planning of strategies to ensure successful implementation and promote the intervention's acceptability to all stakeholders [47].

One invaluable facilitator to our adaptation process was the original developers' willingness not only to report fully both on their intervention development and effectiveness results, but also to personally provide direct support for our study [21, 30]. Another was the accessibility of the original technology (DVD). This allowed frequent quick discussions of adaptations with IT specialists at an early stage, both to transfer the original CISS functions and content to current technology (www.hcvree.ch), and to integrate new content into the existing structure. Also, the CISS intervention's comparatively recent publication offered us two major benefits: 1) It strengthened our eHealth approach by highlighting possibilities for intervention tailoring; and 2) By demonstrating our rigorous maintenance of patient confidentiality, it helped overcome participants' fear of stigmatization [48].

Although we employed open and systematic adaptation processes, the limitations should be acknowledged. To begin with, our contextual analysis was based predominantly on our Swiss setting, and our needs assessment was done in 2015. Since then, this field's evidence base has increased substantially. In this highly dynamic context, continuous adaptation, based on up-to-date knowledge of HCV infection in MSM, will be crucial.

In the meantime, we have also identified evidence in recent articles presenting behavioral interventions targeting sexualized drug use in MSM, e.g., Hugo et al. [49] or Burgess et al. [50]. These researchers' strategies should be considered for further development to strengthen the *HCVree and me* intervention regarding risks of combining drug use with sex. Further, as this intervention is one of the first to specifically target HCV prevention, we are aware that its expansion and adaptation to diverse cultural/national contexts will help identify other needs.

As a strength, although we have made major adaptations, it has not been necessary to alter any of the original intervention's theoretical foundations, i.e., we have been able to

leave key components of its effectiveness in place [41]. And using the adapted *HCVree and me* intervention in the Swiss HCVree Trial will enable an initial feasibility test. As described in the evaluation plan, the outcome and process evaluation results will inform its further improvement [35, 51].

Conclusion

Supplemented by implementation science principles, a systematic approach facilitated adaptations to the scaling-out of an originally HIV-specific behavioral intervention to one aimed at reducing HCV reinfection in successfully treated MSM. If the adapted intervention proves feasible and effective, initial indications suggest that it will be a useful tool against HCV reinfection in this particularly vulnerable group.

While underway, the complexity of the type II scaling-out process was comparable to that of a completely new development. However, it became apparent that we were working with a shifted focus. Building on a well-developed EBI saved us the time and effort of designing a new program, leaving those resources available to incorporate new knowledge and contextual changes into the intervention. This experience strongly supports the scaling-out of proven EBIs.

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Chapter 4. Screening HIV-positive men who have sex with men for hepatitis C re-infection risk: Is a single question on condom use enough? A sensitivity analysis

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4.1 Abstract

Background: Hepatitis C virus (HCV) is common in men who have sex with men (MSM) with HIV. The Swiss HCVree Trial targeted a micro-elimination by using a treat and counsel strategy. Self-reported condomless anal intercourse with non-steady partners was used as the selection criterion for participation in a counselling intervention designed to prevent HCV re-infection. The purpose of this study was to assess the ability of this criterion to identify men who engaged in other sexual risk behaviors associated with HCV re-infection.

Methods: Men who disclosed their sexual and drug- use behaviors during the prior six months, at study baseline, were included in the current study. Using a descriptive comparative study design, we explored self-reported sexual and drug-use risk behaviors, compared the odds of reporting each behavior in men who reported and denied condomless anal intercourse with non-steady partners during the prior year and calculated the sensitivity/specificity (95% CI) of the screening question in relation to the other at-risk behaviors.

Results: Seventy-two (61%) of the 118 men meeting eligibility criteria reported condomless anal intercourse with non-steady partners during the prior year. Many also engaged in other potential HCV transmission risk behaviors, e.g., 52 (44%) had used drugs. In participants disclosing drug use, 44 (37%) reported sexualized drug use and 17 (14%) injected drugs. Unadjusted odds ratios (95% CI) for two well-known risk behaviors were 2.02 (0.80, 5.62) for fisting and 5.66 (1.49, 37.12) for injecting drug use. The odds ratio for sexualized drug use - a potential mediator for increased sexual risk taking - was 5.90 (2.44, 16.05). Condomless anal intercourse with non-steady partners showed varying sensitivity in relation to the other risk behaviors examined (66.7% - 88.2%).

Conclusions: Although condomless anal intercourse with non-steady partners was fairly sensitive in detecting other HCV relevant risk behaviors, using it as the only screening criterion could lead to missing a proportion of HIV-positive men at risk for HCV re-infection due to other behaviors. This work also points to the importance of providing access to behavioral interventions addressing other sexual and drug use practices as part of HCV treatment.

Clinical Trial Number: NCT02785666, 30.05.2016

4.2 Background

In men who have sex with men (MSM) living with HIV, co-infection with hepatitis C virus (HCV) has become a concern over the last twenty years [1]. An HCV RNA-screening of MSM with HIV (n=3722) participating in the Swiss HIV Cohort Study (SHCS) between October 2015 and May 2016 showed a prevalence of 4.8% (n=177) [2]. People living with an HIV/HCV co-infection show faster progression of liver fibrosis compared to people with HCV mono-infection and higher risk for liver-related morbidity and mortality [3]. Since the introduction of the new direct acting antivirals (DAA) cure is possible in 95% of the cases, making micro-elimination of HCV a realistic target [4]. However, the population of MSM with HIV frequently present with HCV (re-) infections and current evidence shows that sexual transmission is one important source of (re-) infection [5]. Addressing sexual risk behavior should become an essential component of HCV medical treatment [6].

In MSM, several sexual behaviors have been described as potentially risky, for example mucosally traumatic sexual behaviors including condomless anal intercourse (CAI), receptive fisting, rectal bleeding, anal douching, sharing of sex toys and group sex activities; nasally applied drugs; injection drug use and drug use in combination with sex [7-9]. Still, to-date, it remains controversial which risk behaviors are the most important ones regarding HCV transmission in MSM with HIV, and should subsequently constitute the most important targets for preventive efforts [10].

From 2015 to 2017, the Swiss HCVree Trial was conducted as an investigator-initiated sub-study of the SHCS using a test, treat and counsel strategy with the goal to eliminate HCV in the MSM population with HIV [11]. An E-health assisted behavioral counselling intervention with nurses as counsellors was developed and implemented with the aim to reduce sexual risk taking. MSM co-infected with HIV/HCV were asked to participate in the counselling intervention if they reported condomless anal intercourse with non-steady partners (nsCAI) the year prior to starting treatment [11]. Condomless anal intercourse was the only risk behavior for which SHCS data was available [12] at the time of intervention development. However, its usefulness in selecting participants for the additional sexual risk reduction intervention remains questionable given that other sexual and drug-using behaviors are also important risk factors for HCV transmission. The current analysis was conducted to investigate the usefulness of nsCAI as the selection criterion for the behavioral intervention. This can provide important information for further studies. Specifically, the aims of this study were to (1) describe sexual and drug-using behaviors participants reported during Swiss HCVree study baseline assessment and to compare those behaviors in MSM who did and did not report nsCAI during the prior year and to

(2) examine the condom-use question's sensitivity and specificity in identifying men who engaged in other HCV relevant risk behaviors and who may, therefore, also benefit from risk reduction interventions.

4.3 Methods

A descriptive comparative study design was used to address the objectives and included a comprehensive assessment of social, medical and behavioral factors. Data were compared for differences between the two groups: those who reported nsCAI and those who denied nsCAI during the prior year.

Setting and participants

The Swiss HCVree Trial was implemented within the framework of the SHCS, an ongoing multi-center prospective observational study that started in 1988. Its participants have been shown to be highly representative of all known people living with HIV (PLWH) in Switzerland, [13] and modelling studies estimate that 84% of all MSM with HIV in Switzerland are followed in the SHCS [14]. During the Swiss HCVree Trial (2015-2017), all adult men with self-identified homosexual or bisexual preferences enrolled in the SHCS (n=3722) were assessed for HCV ribonucleic acid (RNA) [2]. One hundred twenty-two (122) were diagnosed with HCV and treated with DAA in one of eight specialized HIV clinics in Switzerland [11] and all but one individual were cured. Among the men treated with DAA, a positive response to the nsCAI question in the SHCS during the prior year was used to select men who were invited to participate in the sexual risk reduction intervention performed by nurses.

Data collection

The data used in this analysis were retrieved from the SHCS database and the Swiss HCVree Trial baseline assessment. Data included sociodemographic characteristics (age, ethnicity/race, highest completed educational degree) and medical information about HIV from the SHCS database and HCV specific information from the Swiss HCVree Trial. At Swiss HCVree Trial baseline, participants were asked to complete a self-reported questionnaire about sexual and drug-use behaviors during the previous six months. Table 1 summarizes the data collected.

Table 1. Data collected

Database	Domain	Question	Answer
	Variables assessed		
SHCS, reported in interview situation	**Screening question** Selection criteria for sexual risk reduction intervention	"Over the last 12 months, did you have unprotected anal intercourse with occasional partners?"	Yes/no
Swiss HCVree Trial, self-completed questionnaires	**Sociodemographic**		
	Partnership	"Did you have a stable partnership in the last 6 months?"	Yes/no
	Risk Behaviors		
	Sextoys	"Over the last 6 months, did you use sextoys with non-steady partners?	Yes/no
	Fisting	"Over the last 6 months, did you practice fisting?"	Yes/no
	Drug use	"Did you use one or more of the following substances in the last 6 months?"	
		Cocaine	Yes/no
		γ-butyrolactone/γ-hydroxybutyric acid (GHB/GBL)	Yes/no
		Crystal methamphetamine (CM)	Yes/no
		Ketamine	Yes/no
		Mephedrone	Yes/no
		"If your answer is yes, how did you take the substance(s)?"	injection (slammed)/ intranasal/orally/smoked/ mucosally (anal)
	Sexualized drug use	"If your answer is yes, did you take any of the above-mentioned substance(s) in combination with sex?"	Yes/no
	Psychological constructs		
	Attitudes towards condom use	Sexual risks scale-attitudes toward condom use [15] 13 items rated on a 5-point Likert scale	1 (I don't agree at all) to 5 (I completely agree). Possible scores range from 13 to 65
	Condom self-efficacy	Self-efficacy for negotiating condom use [16], 5 items rated on a 1–10 scale	0 (I cannot) to 10 (I am sure that I can). Possible scores range from 0 to 50

Data analysis

Analyses were conducted using the open source R statistical analysis software (Version 1.0.136 for Mac OS X). Participants' characteristics and self-reported at-risk sexual and drug-use behaviors were analyzed descriptively. Depending on the level of measurement and distribution of variables, frequencies, percentages, means and standard deviations (SD), or median and interquartile range (IQR) were calculated. Based on the SHCS data, participants were divided into two groups: those who reported no sex with

non-steady partners or only protected anal intercourse during all sexual encounters during the last 12 months (i.e. without nsCAI) and those reporting nsCAI. Baseline characteristics, attitudes and self-efficacy regarding condom use were compared in the two nsCAI groups. Chi-square tests were used to compare categorical variables and the student's t-test (for age, which was normally distributed) or Mann-Whitney U tests (for years since HIV diagnosis and scores on the attitudes toward condom use and self-efficacy questionnaires, which were not normally distributed) were utilized to compare continuous variables. Odds ratios and their 95% confidence intervals (CI) were calculated to examine the association between nsCAI and the other risk behaviors assessed. Multivariable logistic regression was conducted to determine if adjusting for age and duration of HCV affected the relationship between nsCAI and the other risk behaviors. We used a manual stepwise backward elimination. MedCalc online software (https://www.medcalc.org/calc/diagnostic_test.php) was used to calculate the sensitivity and specificity (including 95% confidence intervals (CI)) of the condom use screening question with non-steady sexual partners in relation to the other at-risk sexual and drug use behaviors.

4.4 Results

During the Swiss HCVree Trial baseline assessment, 118 of 122 participants disclosed their sexual and drug-use behaviors and were included in the current study, see figure 1.

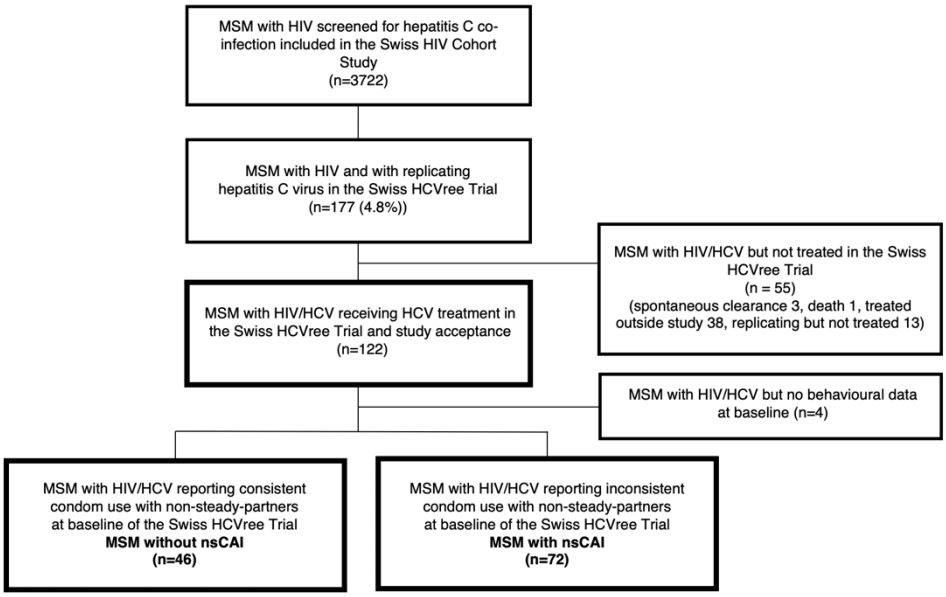

Figure 1: Flowchart Swiss HCVree Trial and group building according to men's response to the nsCAI screening question

Based on SHCS data, 72 (61%) MSM reported nsCAI and 46 (39%) reported no nsCAI during the 12 months prior to enrolment in the HCVree Trial. There were no significant differences in the two groups' socio-demographic characteristics. There were significant group differences in the years since HCV diagnosis; MSM with nsCAI had a shorter median duration of 1.9 years (0.9-5.1) compared to MSM without nsCAI with a median duration of 4.8 years (2.1-10.3). Participants without nsCAI scored significantly more positive attitudes toward condom use and had higher self-efficacy related to condom use than men with nsCAI (median score=44.00 vs. 39.00, p=.023 and median score=40.72 vs. 29.23, p<.001 respectively).

Many men reported engaging in a variety of sexual or drug-use behaviors identified as risk factors for HCV-infection: 25 (24%) shared sextoys, 28 (25%) practiced fisting and 52 (44%) used drugs during the prior six months. In participants who answered the drug-use questions, 44 (37%) reported sexualized drug use and 17 (15%) injected drugs. Participants reported using the following drugs: 30 (26%) used γ-butyrolactone/γ-hydroxybutyric acid (GHB/GBL), 26 (22%) cocaine, 22 (19%) crystal methamphetamine, 11 (9%) ketamine and 10 (9%) mephedrone (Table 2). Those with nsCAI during the 12 months prior to treatment were more likely to have engaged in other risky sexual behaviors than those without nsCAI although the odds in the two groups were only statistically significant for drug use, drug use during sex and injecting drugs. Adjusting for age and/or HCV duration did not change the relationship between nsCAI and the other risk behaviors examined in terms of the direction or significance of the odds ratios.

Odds ratios for two sexual behaviors with established transmission risk were 2.02 (0.80, 5.62) for fisting and 5.66 (1.49, 37.12) for injecting drug use. Sexualized drug use, a potential mediator for increasing other risk behaviors, showed an odds ratio of 5.90 (2.44, 16.05), see table 2.

Table 2. Sociodemographic and HCV-related risk behaviors in the last 6 months at study baseline

Sociodemographic and HCV-related risk behaviors at study baseline	Total (n=118)	Participants without nsCAI (n=46)	Participants with nsCAI (n=72)	Univariable Odds Ratio (95% CI)	Multivariable Adjusted OR (95% CI) for age and HCV duration	Adjusted OR (95% CI) for HCV duration
Age, mean (sd)	46.6 (+/- 9.2)	49.0 (+/- 9.1)	45.1 (+/- 9.1)	0.64 (0.41, 0.96)[a]		
HCV duration, median (IQR)	2.9 (1.1-7.1)	4.8 (2.1-10.3)	1.9 (0.9-5.1)	0.87 (0.80, 0.94)		
Sharing sextoys, n (%) (n=104/38/66)[b]	25 (24)	7 (18)	18 (28)	1.53 (0.58, 4.40)	1.05 (0.36, 3.21)	1.08 (0.37, 3.29)
Fisting, n (%) (n=114/43/71)[b]	28 (25)	7 (16)	21 (30)	2.02 (0.80, 5.62)	2.12 (0.78, 6.31)	1.92 (0.72, 5.60)
Drug use, n (%) (n=117/45/72)[b]	52 (44)	8 (18)	44 (61)	7.27 (3.08, 18.91)	5.58 (2.26, 15.02)	5.79 (2.37, 15.42)
GHB/GBL, n (%)	30 (26)	3 (7)	27 (38)	8.60 (2.78, 37.87)	6.64 (2.04, 30.18)	6.91 (2.15, 31.07)
Cocaine ,n (%)	26 (22)	6 (13)	20 (28)	2.56 (0.99, 7.55)	2.36 (0.85, 7.39)	2.49 (0.91, 7.6)
Crystal methamphetamine, n (%)	22 (19)	1 (2)	21 (29)	18.48 (3.63, 338.0)	15.47 (2.89,288.31)	15.91 (3.01,294.78)
Ketamine, n (%)	11 (9)	2 (4)	9 (14)	3.12 (0.76, 21.14)	3.55 (7.82, 25.71)	3.55 (7.82, 25.71)
Mephedrone, n (%)	10 (9)	-	10 (15)			
Use of any of the drugs listed above during sex, n (%) (n=116/45/71)[b]	44 (38)	7 (16)	37 (52)	5.90 (2.44, 16.05)	4.42 (1.73, 12.52)	4.63 (1.84, 12.92)
Reporting injection of drugs, n (%) (n=117/45/72)[b]	17 (15)	2 (4)	15 (21)	5.66 (1.49, 37.12)	4.45 (1.10, 30.15)	4.53 (1.13, 30.51)

[a]Unit 10 years

[b]specified how many HIV-positive MSM answered the question (n=total group/without nsCAI/with nsCAI)

Table 3 summarizes the results of analyses examining the sensitivity and specificity of reporting consistent condom-use with non-steady partners at study baseline in identifying men who did not engage in the other at-risk behaviors examined. The nsCAI question had the highest sensitivity in relation to the question about injecting drugs (88.2%) and lowest for sharing sex toys (66.67%). Specificity was low in all analyzed risk behaviors (41.18%-57.58%).

Table 3. Sensitivity analysis of screening question "nsCAI" to identify other probable risk behaviors for HCV re-infection

Risk Behaviors	Sensitivity† (%) (95% CI)	Specificity‡ (%) (95% CI)
Any drug use	84.62 (71.92-93.12)	57.58 (44.79-69.66)
Sexualized drug use	84.09 (69.93-93.36)	52.70 (40.75-64.43)
Injecting drug use	88.24 (63.56-98.54)	43.56 (33.72-53.80)
Fisting	75.00 (55.13-89.31)	43.18 (32.66-54.18)
Sharing of sex toys	66.67 (48.17-82.04)	41.18 (30.61-52.38)

†The probability that HIV-positive MSM report a selected risk behavior will also report nsCAI

‡The probability that HIV-positive MSM will deny nsCAI if they are not engaging in other selected other risk behaviors.

4.5 Discussion

The MSM co-infected with HIV/HCV in this study practiced various sexual and drug use behaviors associated with HCV transmission risk in addition to condomless sex. While nsCAI was associated with higher odds of engaging in other behaviors, based on our findings, relying only on this question to identify men at risk for HCV re-infection is likely miss a proportion of MSM with HIV at risk for HCV due to other behaviors. Between 16% to 18% of the men who denied nsCAI reported engaging in other behaviors that have been associated with an increased risk of HCV re-infection. Eighteen percent (18%) of those who denied nsCAI reported using drugs. This is an important finding as drug use is seen as a potential mediator for increased sexual risk-taking [17, 18].

Condom use was the only risk behavior available for all men in the SHCS and was for this reason used as the criterion for selecting men to participate in the sexual risk reduction behavioral intervention portion of the Swiss HCVree Trial [12]. Despite our use of this inclusion criterion, its discriminatory value in identifying men at high risk for HCV re-infection was unclear. However, a recent study from London found that CAI was a significant risk factor for acute HCV infection in MSM and in one third of participants it was the only risk factor [9]. In contrast to our study, MSM received care in a sexual health clinic and benefitted from a multi-disciplinary prevention approach including harm reduction services whereas in our study, HCV treatment was given in specialized medical HIV clinics. In line with other investigations in MSM with HIV, study participants reported various behaviors other than nsCAI that potentially increased their risk of HCV sexual transmission [9]. It has been well documented that condoms are less attractive in the MSM community – largely due to the common understanding and awareness that HIV treatment is preventive in terms of HIV transmission [19]. Decreasing trends of condom use

was confirmed in a systematic review of studies across high-income countries [20]. Champenois et al. [21] reported that for MSM with HIV the main reasons for not using condoms were serosorting and being on antiretroviral therapy (ART) with undetectable viral loads. While these traditional HIV-related risk reduction strategies (serosorting and effective HIV treatment) have been shown to prevent the transmission of HIV, they have little or no effect in preventing HCV or other sexually transmitted diseases.

In our study, MSM with HIV and nsCAI were more likely to engage in other risk behaviors compared to those without nsCAI but the relationship was only statistically significant for drug-use and sexualized drug-use. However, due to the small sample size, our study was probably only adequately powered to detect large differences in the groups. They were two-times more likely to practice fisting and six times more likely to report sexualized drug use. The sensitivity of the nsCAI question was 85% in relation to drug use. Nevertheless, our findings indicate that using nsCAI as the only risk behavior criterion to select men for the behavioral intervention was likely to have resulted in failure to include between 12% and 34% of those engaging in other risk behaviors. Each single behavior included in the current analysis carries a specific HCV transmission risk; however, which behavior or combinations of behaviors carry the highest risks is currently less clear and cannot be answered with this study design.

Our results are in line with other studies showing associations between higher rates of drug use/sexualized drug use and risk behaviors [17, 22, 23]. A substantial proportion of our participants reported drug use (44%). Among the men who answered these questions (116 for sexualized drug use and 117 for injecting drugs), 38% reported sexualized drug use and 15% reported injecting substances. In comparison, in two earlier studies on MSM with HIV– one from Madrid (n=742) [22] and one from England/Wales (n=392) [23] 29.1% – 29.5% of participants indicated sexualized drug use and 10.1% – 16% injecting drug use. Our group's higher rate of sexualized drug use might reflect differences in the study population, especially the fact that our sample's MSM with HIV were all co-infected with HCV. Several studies have found elevated rates of sexualized drug use in MSM co-infected with HIV/HCV, affirming associations between sexual HCV transmission and higher risk taking behaviors when using substances [24, 25]. Another possible explanation for our group's high rates of sexualized drug use may be related to the study setting: most of our participants were recruited at the centers in Zurich, a town known for a comparably high prevalence of sexualized drug use. In the European MSM Internet Survey (EMIS-2010), which compared 44 European cities in relation to illicit drug use in MSM, place of residence was the strongest predictor. Zurich reported a 7% prevalence of using one of the four drugs typically used during sex, ranking sixth of the 44 cities

studied, just after UK and Spanish cities [26]. In another European survey conducted among MSM in 13 cities, overall prevalence of sex associated with drug use was 11.8% (when measured at the last sexual encounter), and was more frequently reported by MSM with HIV [27].

The four substances typically used during sex were all reported in our study, with GBL/GHB being the most common (25%), followed by crystal methamphetamine (19%). In EMIS (European MSM Internet Survey), percentages of GBL/GHB use were quite similar, but crystal methamphetamine use was lower [26]. than in our study, suggesting a surge in its popularity in MSM with HIV. The frequency of cocaine use was also high (22%) – comparable to rates reported in the UK ASTRA trial in MSM with HIV or for Zurich in EMIS [17, 26]. To date, few studies investigating sexualized drug use have included cocaine. However, our results indicate that cocaine may be more common (19%) in sexual contexts than expected.

This study has several limitations. The study's cross-sectional design precluded any causal inferences about the associations between nsCAI and other behaviors risky for HCV re-infection. During analysis, we identified some limitations in the formulation of questions, e.g., we did not ask about the distinction between insertive or receptive fisting. While self-report questionnaire data may be biased, especially for such sensitive domains as sexual and drug use behavior, it is often perceived as superior compared to being asked by someone else because of reduced social desirability bias [28]. Given the limited number of MSM co-infected with HIV/HCV in Switzerland, the study sample (118 participants) was small. The small sample size may have limited our ability to detect statistically significant differences in behaviors in the nsCAI and non-nsCAI groups that were clinically meaningful. One strength of the study is that the Swiss HCVree Trial (the source of data for this study) screened and treated all participants co-infected with HCV in the SHCS, so the sample is likely to be representative of MSM with HIV living in Switzerland [13].

Conclusion

Our findings support existing research that MSM co-infected with HIV/HCV engage in various sexual and drug-use behaviors, potentially increasing their risk of HCV re-infection. Men who reported using condoms inconsistently with non-steady partners were more likely to report engaging in the other sexual and drug-use

behaviors measured although the differences were only statistically significant for the drug-use behaviors. nsCAI was fairly sensitive in identifying men who also engaged in other risk behaviors, but relying only on it to identify men at risk for HCV infection would miss a proportion of MSM with HIV practicing other potentially modifiable behaviors. Based on our findings we recommend comprehensive screening of potential risk behaviors to identify men whose sexual and drug use behaviors increase their risk for HCV infection. We recommend offering all MSM co-infected with HIV/HCV behavioral interventions designed to reduce sexual and drug use risk behaviors.

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Chapter 5. "Giving hepatitis C a place and living without it again": Sense-making in a sexual risk reduction intervention in HIV/HCV co-infected men who have sex with men. A reflexive thematic analysis

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5.1 Abstract

Hepatitis C virus reinfections in HIV-infected men-who-have-sex-with-men (MSM) challenge individual as well as public health effectiveness of antiviral treatment. We evaluated the response to a sexual risk reduction intervention within an HCV-treatment trial. Seventeen intervention-participants were recruited for semi-structured interviews that were analyzed with reflexive thematic analysis.

The constitutive theme of *Giving hepatitis C a place and living without it again* illustrates how participants positioned themselves regarding the program and their sense-making work with it thereafter. We account for differences in participants' sense-making work, by a description of three groups: 1) *Avoid risks: get rid of hepatitis C for life,* 2) *Minimize risks: live as long as possible without hepatitis C* and 3) *Accept risks: live with the risk of hepatitis C*.

This study shows that unpacking responses to an intervention program is valuable. This qualitative evidence helps to tailor interventions to reduce reinfections and to reach an optimal impact.

5.2 Background

Today, chronic hepatitis C virus (HCV) infection can be easily cured with effective direct acting antivirals (DAA), leading to enhanced survival, less liver-related morbidity, improved quality of life, and prevention of extrahepatic complications [1-5]. Since the introduction of DAA, many HIV-infected men who have sex with men (MSM) have undergone successful DAA treatment, but were re-infected within a median of 100-500 days after achieving sustained viral response (SVR) [6, 7].

In Switzerland, MSM with HIV showed an 18-fold increase in HCV infections between 1998 and 2011, peaking in approximately 20 new infections per year [3]. They have been targeted as a key population for multiple HCV prevention strategies [8]. The Swiss HCVree Trial was launched to test a micro-elimination strategy in this population [9]. The study was conducted irrespective of DAA restrictions existing at the time: high medication costs had led to treatment being reserved only for patients with advanced liver fibrosis or cirrhosis [10]. In this trial, HIV-diagnosed MSM who were participating in the Swiss HIV Cohort Study (SHCS) [11], were systematically screened for HCV RNA and an additional interventional strategy was used combining treatment with a behavioral intervention [10]. The intervention's aim was not simply to scale up HCV treatment, but also to reduce HCV incidence and to avoid reinfections [12].

At the time of the Swiss HCVree Trial's preparation, behavioral interventions targeting MSM focused predominantly on the risk of contracting or transmitting HIV. Targeting sexual risk behavior linked closely to HCV-transmission in the subgroup of HIV-infected MSM potentially at risk for HCV reinfection would require new approaches. Particularly sexual practices leading to mucosal trauma, e.g., chemically prolonged receptive intercourse, receptive fisting, receptive use of sex toys, anal douching, group sex and the sharing of snorting drugs in such contexts, have been shown to be strongly associated with HCV infection [13-18]. Also, increases in sex-related recreational drug use has put MSM at highest risk for HCV infection, e.g. sharing of injection equipment in sexual contexts or having an increased potential for anal or rectal trauma due to longer and more intense sexual encounters with multiple partners [13, 19-22]. In addition, over the last decades, HIV-diagnosed MSM have increasingly engaged in sexual contacts with other HIV-diagnosed MSM to reduce HIV-related stigma, leading to a higher likelihood to be exposed to HCV [23]. And since 2008, the increasing awareness that persons under successful antiretroviral treatment for HIV are virtually non-infectious, known as 'Swiss Statement' [24], or meanwhile more broadly known as U=U, has led to ongoing decreases in condom use [25, 26]. Based on a growing body of related studies, we adapted an evidence-based counselling intervention to improve self-regulation of risks associated

with specific sexual behaviors and sexualized drug use. We implemented this in parallel with HCV treatment [27].

To gain a better understanding on how to further adapt the behavioral intervention for effective intervention scale-up, we conducted a quantitative evaluation of the program's effectiveness and a qualitative evaluation of participants' experiences with the program [28, 29]. Here we present results of the qualitative evaluation conducted 6-12 months after participation in the program and focused on exploring the intervention program's meaning for men regarding their sexuality.

5.3 Methods

We followed Braun and Clarke's reflexive thematic analysis approach [30, 31], using a constructivist orientation. The principles of constructivism allowed us to explore individual experiences in order to better understand the various subjective belief systems [32]. These constructions helped us to understand participants' sense-making of their intervention program experiences [33], as well as to identify patterns, themes to uncover commonalities and differences within the participants' sense-making processes [34].

Setting and sampling

This study was embedded in the Swiss HCVree Trial [35]. Between 2016 and 2017, 122 HIV/HCV co-infected MSM, all participants of the SHCS, accepted the offer of receiving free DAA treatment in one of seven specialized HIV outpatient clinics across the country. MSM who reported inconsistent condom use for anal sex with non-steady partners the previous year (n=72) were invited to participate in the behavioral intervention [36]; fifty-one additionally accepted to take part, and were therefore eligible for this qualitative study.

We used a purposive sampling approach with the aim to include a diverse range of participants [37]. We included MSM a) of various ages, b) across a broad range of years since their HCV and/or HIV diagnosis, c) with various numbers of HCV treatments, d) receiving treatment at various treatment clinics and e) with various levels of experience with counsellors. Potential participants were recruited by their responsible clinicians. Of 51 intervention participants, 21 were invited to participate in the interviews, of whom 17 agreed and provided written informed consent. In all cases, the reason given for non-participation was lack of time.

The behavioral intervention

HCVree and me is a theory-based intervention using an adapted version of the information-motivation-behavioral (IMB) skills model [38, 39], social cognitive theory (SCT) [40], the trans-theoretical model (TTM) [41] and theoretical aspects of cognitive neuroscience. The intervention consisted of four individual eHealth-assisted counselling sessions, planned for treatment weeks 4, 6, 8 and 12. The counselling was carried out by trained nurses using motivational interviewing techniques.

The first session focused on exploring participant's emotions and values regarding sexual behavior. This process was guided by video clips presenting case vignettes of relevant emotional situations. A selection of 13 video clips was available of which the participant could choose 1–3 that were most appropriate to further reflect and to relate to their personal experiences. The second session focused on perceived benefits and disadvantages of the participant's specific sexual conduct. This was also supported by videoclips and interactive information (regarding, e.g., what do we know about HCV risk factors?, what means safe substance use?). The third session focused on setting individual goals for behavior change. In the fourth and final session, these goals were used to reassess and adapt initiated change processes.

Data collection

Data were collected via semi-structured individual interviews 6–12 months post-intervention (end of treatment and behavioral intervention). The interviewers used an interview guideline with open-ended questions about participants' experiences with and perceptions of the intervention (e.g., *"If you think back, what do you remember of the behavioral program and why?"*). We first stimulated participants both to describe notable situations they experienced during the intervention, and later to reflect on any thoughts, emotions and behaviors that they perceived in relation to the program. Based on the participants' responses, the interviewer then delved into topics such as their experience of living with HCV and/or HIV, of HCV treatment, their HCV cure, and their former or current sexual risk behaviors.

Four female researchers (PKH, KF, MR, DN) conducted the individual interviews. All were academically trained nurses with experience in qualitative data collection and were involved in intervention development and/or were counsellors in the Swiss HCVree Trial. Interviewers' strong knowledge of the behavioral intervention [34] allowed them to facilitate participants' reflection on—rather than a simple description of—the intervention. However, it was important that the interviewers had no former relationship with any of their interviewees (nor as a counsellor). Starting data analysis already after the first three

interviews allowed us to work iteratively include new questions based on the results of preliminary analyses. Individual interviews lasted 37–77 minutes (mean: 48). According to participants' preferences, 11 interviews took place at the outpatient clinic and six at the interviewees' residences. All interviews were audio-recorded and transcribed verbatim.

Data analysis

We followed Braun and Clarke's six-phase reflexive thematic analysis approach [30, 31], our main analytical goal being to discern shared meaning-based patterns in participants' responses to the intervention.

Analysis began with familiarization with the data (phase 1). After carefully reading each transcript, two researchers (PKH/DN) discussed their initial notes, which they summarized in visual maps including summaries with preliminary conceptual definitions. In phase 2, the first author began coding the data. Conferring regularly with the co-authors, the process was reflective and advanced: we quickly identified several initial themes (phase 3). Based on analytical memos and input from our discussions, these preliminary themes were continuously elaborated and adapted (phase 4). Via systematic review and comparison with our source data, we confirmed emerging thematic patterns, and further identified subtle but important differences between participants (e.g., some men spoke about behavior changes before counselling started, others did not; differences in the perceived severity of HCV infection). To account for these, we constructed groups illustrating the diversity of sense-making work in relation to the intervention. In phase 5, we discussed the thematic pattern several times within the research group, involving one patient representative who was not a study participant, at institutional research meetings. Feedback from these discussions led to refinement of the thematic pattern. Finally, during phase 6, two researchers (PKH/DN) produced the report, again making minor changes to improve its overall coherence. We used the software MAXQDA Plus 2018, version 18.2.0, for analyzing the transcripts.

5.4 Results

Six to twelve months after the intervention ended, 17 participants reported on their experiences with it and what it meant to them. These men were between 28 and 69 years of age, with a median of 44 years (interquartile range (IQR): 41-53). They had known of their HIV infection for a median of 10.9 years (IQR 6.5-17.3) and of their HCV infection for a median of 1.6 years (IQR 1.2-4.1). Six had had experience with the earlier Interferon-based therapy prior to DAA treatment. Three who had their HCV infection cleared

by this therapy were participating in the Swiss HCVree Trial for treatment of HCV reinfection with DAA.

The interviewees' various life situations and experiences with chronic HCV infection and its treatment, especially the current therapy within the Swiss HCVree Trial, had an impact on how they experienced the intervention program. Accordingly, we first describe the identified constitutive theme of *Giving hepatitis C a place and living without it again.*

Giving hepatitis C a place and living without it again

Giving hepatitis C a place describes how the men approached the behavioral intervention. This was influenced by their understanding of the transmission and consequences that this chronic infection would have on their lives. In addition to their experience of using DAA within the study, the behavioral intervention altered their perceptions. And in *Living without it again,* they describe the behavioral intervention program's perceived impact and how participants felt—especially with respect to estimating the risk of a possible reinfection—after being cured.

For all interviewed men, being diagnosed with hepatitis C was unexpected. They reported how they tried to understand not only how they became infected, but also the disease's severity and its meaning to them. This was important to enable them to cope with the risk of transmission. While some described an explanation they considered valid, others reported lasting uncertainty, especially with respect to transmission. One 52-year-old man said:

> So for me, there were three relatively surprising infections. And so therefore maybe I had more of a need than others, to explore where that could have come from. Sure, there is always the risk component. But in my mind, I don't find that part of it so large. And that's why it's not understandable to me.

Later the participants reported that, when they agreed to the behavioral intervention, they did not expect to profit personally from it. Some had explicitly asked for the right to quit (which was, of course, available to all). However, all reported positive experiences of feeling directly and personally addressed during the program both by the nurse counsellor research team and by the content. Several participants were surprised that they could reflect seriously on themes that were relevant to them in a way that helped them to better understand their own infections and behavior. A 42-year-old participant expressed this experience as follows:

> In many discussions, it was really about me. It was about understanding myself! And what I really want to do. [...] No one said, you should do this or that—not at all! And that was something new.

Yet, not only the intervention sessions were important to these men: the experience of being cured of hepatitis C, which ran in parallel, was obviously also important; but not necessarily interpreted in a positive way: Some reported that the cure evoked a feeling of personal vulnerability with respect to a possible new infection with HCV and they had to learn to cope with this. A 54-year-old man explained:

> I have to deal with this whole crap again. Now one has to be careful again. So a lot of stuff came up again. A lot of dark stuff and fears. And yeah, almost a little of the feeling that I don't go through this again.

While the constitutive theme of *Giving hepatitis C a place and living without it again* was central for all of the men, three main explanatory models emerged from the data, reflecting the wide range of individuals' belief systems and sense-making, which were influenced by participants' different contextual realities (see figure 1):

1) *Avoid risks: get rid of hepatitis C for life;*

2) *Minimize risks: live as long as possible without hepatitis C;*

3) *Accept risks: live with the risk of hepatitis C.*

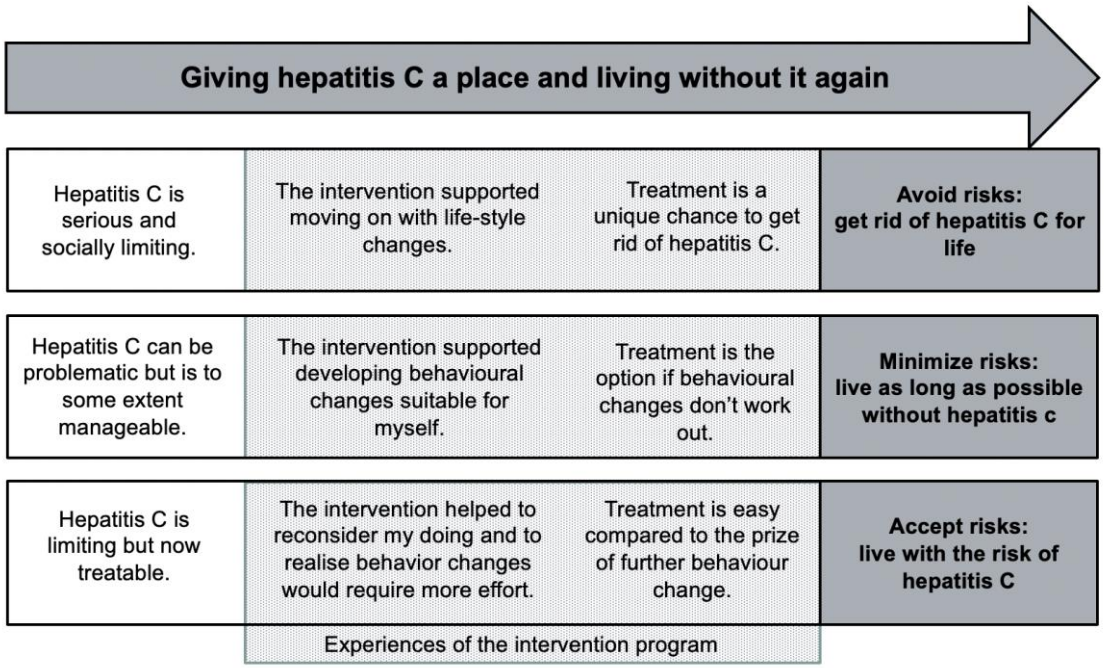

Figure 1: Overview of our constitutive theme and the three groups to account for the diversity in participants' sense-making work

1. Avoid risks: get rid of hepatitis C for life

Avoid risks: get rid of hepatitis C for life refers to a sense-making work shared by men who regarded hepatitis C as serious, and who took active steps to modify their risk behavior, even before beginning treatment and counselling. Having experienced the intervention as supportive within the process of lifestyle changes they had already started, they aimed to avoid risks to get rid of hepatitis C for the rest of their lives.

Men who used this sense-making work saw themselves confronted with an illness they had not even considered before their diagnosis. They reported considering HCV infection as something alien—a virus relevant for drug addicts, but not for them. The diagnosis forced them to think seriously about hepatitis C, to identify risk situations to which they had exposed themselves and to realize how their infection could be explained. A 52-year-old man said:

> Where in the past you went wild with drugs, in the scene, drugs and party culture. Where night after night you took Ecstasy and went wild nights dancing. And then of course you had a relatively large number of sex partners, which changed up a lot. That was before [current] relationship.

They assigned these risk situations to time periods characterized by carelessness and eagerness to experiment sexually. Three gave particularly noteworthy reports of their former lifestyle adjustments—of how they cut the risks partly because of their hepatitis C diagnoses and partly due to entering a partnership. As all but a few had received their diagnoses before any reliable therapy became available (median time since diagnosis: 5.8 years) most had tried to come to terms with the thought that they carried a serious communicable chronic condition.

For many, from the moment they were diagnosed*, "Hepatitis C was always in...[their] head[s]."* It was a *"serious and socially limiting problem."* For example, *"HepC gobbles up energy",* leads to liver damage, and poses a huge problem for the partner because of the danger of transmission.

These men embraced the possibility of being cured as indescribably wonderful. They viewed the DAA as *"a stroke of luck", "an immense chance."* A 45-year-old man said *"the therapy has given me a new life."* Even after study screening and before treatment started, this group's appreciation appeared to motivate them toward independent behavioral changes. Two men had already tried to practice protected sex with multiple partners or to stop sexualized drug use because they had observed themselves becoming more reckless. Two others said they had stopped all sexual contact when their participation in the trial began.

Upon entering the intervention, based on their intensive early thoughts about hepatitis C and their behavioral changes, their attitude was: *"If it doesn't help, it at least won't make things worse".* After all, they already had considerable knowledge and did not expect any personal gains. Many related how they had been positively surprised by the intervention, perceiving it as an environment in which they felt personally cared for and understood in their challenges regarding sexual risk behavior.

This is how a 28-year-old man described it:

> It [the counselling] was very informative and what did it bring? You also thought about yourself again a little, that had maybe gotten a little lost lately. And it was also nice somehow to know, that there are people who are at all interested. And that is for me also a nice aspect of the story.

At the time of the intervention, the men generally felt they were already moving in the right direction but wanted to achieve and maintain *"the strict practice of safer sex"* over time. In the long run, they saw absolute avoidance of risk as the only way to maintain their health. This is why they used the intervention to discuss situations that were awkward and difficult for them—with the intention of being better prepared.

They also appreciated that during the intervention, according to their own personal interests, they could decide the direction discussions should go. Among the intervention's other benefits, they appreciated the opportunity it offered to reflect on their *"previous high-risk sex life"*—the lifestyle that had led them to acquire the disease. They recognized during the interview that they saw their experiences with risks as something useful and now as an important resource in the current situation. A 39-year-old man described the effect of his experiences as:

> The light went on for me. In the sense of just thinking before you do something. Before, I didn't have any knowledge of where you can get hepatitis C. You simply go too far and now you say to yourself: I won't let it go so far again.

A general consensus among participants was that the behavioral intervention as well as the successful treatment had reinforced their intention to build on and maintain the lifestyle changes they had already made. For them, using condoms for anal intercourse, avoiding mucosal trauma and the avoidance of drugs best possibly made sense: they saw the cure of their hepatitis C as a unique chance and decided to avoid any contact with the virus in the future. They experienced the cure as liberating, felt relieved and happy.

One described it as *"a success that [he] was permitted to experience thanks to the therapy."* They considered a reinfection as a personal failure, as a disgrace against themselves and also against their doctor. One 45-year old man described how the risk of reinfection is a source of fear and led to increased caution after cure:

> It was strange in the beginning after the treatment. I was overly careful. I wasn't even able to enjoy it, because I was afraid. That it turned out so well [positive] and that I don't have it anymore. That was always a topic.

Men in this group said that their only hope for being free of HCV was to *avoid risks.* Therefore, they had resolved not to expose themselves to any further risks. Their shared goal was never to be infected with hepatitis C again—to *get rid of hepatitis C for life.*

2. Minimize risks: live as long as possible without hepatitis C

This theme showed a sense-making process prevalent in men who experienced hepatitis C as a problematic but manageable disease. They described the behavioral intervention as helpful to facilitate thinking about risks and how to develop behavioral changes suitable for their aim of living well with long hepatitis-C-free periods.

Compared with the first group, these men had only recently become aware of hepatitis C (median time since diagnosis: 1.6 years), with diagnoses received, in most cases, during regular STI testing. Unlike the earlier group, they had vague knowledge of hepatitis C, but had hardly paid attention to it until they were diagnosed themselves. Their diagnoses had typically come as a surprise because they did not consider themselves, compared to their peers, as being high risk. Their diagnoses had made them uncertain of how to gauge the relative risks of various behaviors. They concluded that they must have contracted the virus in an exceptional situation. They further said that they had practiced condomless anal sex with multiple (HIV-positive) partners for years. Since the hepatitis C diagnosis was first made many years later, they concluded that this behavior couldn't be particularly risky and were uncertain about how to protect themselves and others, described by this 54-year old man:

> [I regularly participated in sexual practices] without a condom. I did it like this for a long time before that, and hepatitis C didn't happen, until 2015. The, I think I surely didn't use them for ten years. And I had unprotected sex just as often during these ten years.

Like the earlier group, the men in this group were concerned about infecting their sex partners. Unlike that group, however, they adhered to their original explanatory model—that they had contracted HCV during a single exceptional situation—and did not report any adaptation prior to the start of the intervention program.

Also like the first group, these men were pleased to take part in the study, and to receive the highly-effective and expensive medication free of charge. They said that when they learned of the new DAA treatment, which was both simpler and more effective than

Interferon-based treatment, they concluded that *"hepatitis C can cause issues that are to some extent manageable."*

Unlike the earlier group, these men agreed to the intervention mainly because they saw it as a possibility *"to return something because [they were] receiving DAA with voluntary participation."* Some also hoped to learn more about hepatitis C through their participation:

> The knowledge, that's what I was looking for. The knowledge about this, also in our community, is not really succinct or firmly understood. And for that reason, the probability of taking risks is much higher.

They said they had enjoyed the behavioral intervention. In addition to the medical treatment, they appreciated the possibility of talking to a highly-knowledgeable nurse counsellor who did not judge them. For this group, the knowledge gained during the intervention was a sudden insight. They were impressed by the fact that various situations could result in infection — for example, shared use of anal douches (a common practice by MSM before anal intercourse) or tubes for intranasal drug consumption. From the information they received, they concluded that one of the intervention's main messages was that *"HepC is easy to get and can also return."* One even described the virus as particularly *"malicious".*

Another difference between this group and the first was that the behavioral intervention first motivated them to reflect on their own sexual preferences and the associated risks. They reflected on their personal risk situations with the counsellor and openly discussed possible changes to their behavior.

Their sessions with the counsellors supported them in their choices for or against certain changes in behavior – a dynamic reflected clearly in their perception of practicability. For example, this group did not see regular condom use as feasible, because they did not feel ready. Instead, they chose changes they considered easily made, such as *"use gloves when fisting in a save way"* or *"not sharing my sex toys with other people."*

Regarding behavioral changes, this group also showed less categorical positioning than the first group, adhering instead to the strategy of *"choosing behavioral changes suitable for myself."* They felt that the intervention supported them in the sense of maintaining feasible behavioral changes. Some said they participated less often in sex parties, opting instead to organize non-sexual leisure weekend with friends to provide for diversion. Others cut back on their drug consumption by carrying less money with them, or by deleting their dating apps to avoid spontaneous blind dates. One explained:

> With the life I lead, it [the risk] can only be minimally reduced. And I'd rather have, for example, one encounter less and with that have the risk only once instead of twice. Rather that, than say I'll use a rubber and then not have any fun anymore.

This group, too, was tremendously impressed by the effectiveness of the new medical treatment options. However, if the behavioral changes they made were insufficient to prevent reinfection, these men could definitely imagine another round of medical treatment as an option. Aware that they were only partially changing their risk behavior—and that this might not be enough—they changed what they believed was feasible. One participant explained:

> What I want or should do, I am absolutely still aware. I knew it before, but the program has created more awareness. But I am not so good at implementation, or actually not good at all so to say. But I do think, I do some of the things, but just not all that I have wanted to do.

For this group, reducing risk contributed importantly to living as long as possible without hepatitis C. Having chosen to *minimize risks (to the best of their ability)* they knew this strategy left them vulnerable to reinfection. Compared with the first group, they made few compromises, but hoped to *live as long as possible without hepatitis C*.

3. Accept risks: live with the risk of hepatitis C

The third theme referred to the sense-making work in men who were highly concerned of hepatitis C for fear of sexual rejection. They described the intervention as useful to reconsider their own sexual risk behavior and to realize that further behavior changes would require more efforts to avoid reinfection- in contrast to medical treatment perceived as "easy". In this sense, they expected to undergo repeated rounds of treatment or stay HCV re-infected if necessary.

As in the second group, men with this sense-making style had only known of their hepatitis C infection a relatively short time (median 1.5 years); however, as in the first group, the diagnosis had elicited an independent, active and intensive search for information to explain and understand the infection. Two stated, for example, that they had already undergone at least one successful Interferon-based therapy and that they had then sought information to allow them to consciously protect themselves against reinfection. Based on the extent of their knowledge at that time and how they viewed the first infection, they had decided on certain behavioral changes, such as "*avoiding fisting"*. Two men living together as partners reported other experiences. As both had HIV/HCV co-infection, they saw no need to change their behavior. They described their joint status even as a relief. They could set the topic of hepatitis C aside:

> What was easy for us, was that we had the same thing. He was positive [HIV and HCV] and me, too. That's why we got together, because we supported each other. Because how do you want to find a life partner that doesn't have it, that doesn't understand the problems? We complemented each other well. We each respected each other, showed affected to one another, supported. It was just as hard for him probably to find a life partner, as it was for me. Someone that accepts and takes you as you are.

Among the men in this group, attitudes toward behavioral intervention reflected their personal, intense searches for hepatitis-C-related information prior to the study. Similar to the first group, they did not expect much of the behavioral intervention and mainly participated to please their medical doctor. Having already gained considerable knowledge and had practiced changing some of their behavior, though, they did not see themselves as the right people for an intervention. Unlike the first group, but analogous to the second, they had not tried to completely eliminate the risk of reinfection but had selected easy risk-reduction adaptations. Two men who contracted HCV reinfections despite such changes were dumbfounded. As this 46-year-old man said:

> When you can't pin it [the infection] down – you know, I mean – the first time it was so nice, because I knew exactly where it [hepatitis C] came from, where I got it, from whom. I knew out of which situation it came. Then it's easy to say: Ok, I'll change something. But when later, I stand there and the liver values are high and I can't link it to any specific situation, then it's difficult to change anything.

These men did not use the intervention primarily to learn and expand their knowledge, but rather as a place where they could openly talk about past difficult situations and about their failures. Thus, they talked with the counsellor, for example, about difficult experiences in disclosing their HCV status. They saw this as an important preventive measure but found it difficult because of the rejection they experienced as a result, described by this 56-year-old men:

> It's hard to change much. Because in the moment you don't want to talk about it. Because that's when you want to party, have sex, you want to enjoy and you don't want to say, he stop, hepatitis C, then everything would be over.

The men in this third group saw little possibility of protecting themselves more effectively in the future: similar to the second group, they considered strict use of condoms, monogamy or even total rejection of sexualized drug use as effective protective measures, but they felt that such adaptations were too extreme and difficult. This was described particularly succinctly by one participant—a self-professed *"sex and drug addict"*—who acknowledged that the intervention made sense but was not intensive enough for his needs.

This group saw only one feasible restriction option: "having fewer sexual encounters." Unlike the second group, they had no illusions: they knew how easily they could be infected with HCV, but insisted on continuing risky "non-negotiable behaviors" and expected to be re-infected at any time. One man called this approach *"Russian roulette."* These men considered the new DAA a good and important option compared to the challenges of behavioral change. One 54-year-old man exemplified this attitude:

> That would probably also go in that direction with hepatitis C. That it will become less expensive to treat and then it becomes even less a topic for some people, like myself, to think about having sex with a condom.

They spoke of the great benefit of successful therapy —*"the liver gets a break."* At the same time, though, the cure appeared to elicit ambivalence. While it greatly decreased their potential liver-related morbidity, it also meant *"having to watch out again"* One described it anxiously as *"feeling put back to the time with HIV before the [2008] Swiss Statement"*.

Thanks to the availability of curative therapy, they hoped that all MSM would regularly be tested for HCV and, if infected, receive treatment. They were convinced that this would reduce the danger of HCV infection for their sexual partners. Having rejected major behavioral changes, they intended to *live with the risk of hepatitis C, i.e*., they believed their only reasonable course of action was to a*ccept the risks.*

5.5 Discussion

With this study, we added to the understanding on how HIV/HCV co- and/or re-infected men responded to one of the first HCV-specific sexual risk reduction intervention implemented in combination with medical treatment with DAA. Results show participants' processes of positioning themselves to the program and their sense-making with the intervention thereafter. We identified three kinds of sense-making work which helped to summarize the variety of responses and highlight individual sexual risk reduction-appraisal, decisions, strategies and challenges.

We interpreted the qualitative data with an eye on how men used their experiences with this behavioral risk reduction intervention. Early in in the process of data analysis, we recognized the influence of previous experiences such as diagnosis and the experience gained through participation in the intervention program including both behavioral counselling and DAA on risk appraisal and decisions for behavioral changes. In order to strengthen our interpretation, we introduced the concept of sense-making using

Mamykina et al.'s definition: "Sensemaking is how individuals make sense of complex social dynamic environments and phenomena, construct mental representations of these phenomena, and use these representations to guide their action" [42]. According to this definition, sense-making can be understood as an ongoing process, triggered by new situations, after which person's use their knowledge or developing ideas to react to new situations [43]. This facilitated our development of a constitutive theme, accounting for pre- and post-intervention experience. More concretely, the concept of sense-making first captured the groups' shared meaning-based patterns, then highlighted the inter-group variation.

The constitutive theme of *Giving hepatitis C a place and living without it again* illustrates the continuum of sense-making with the intervention program influenced by two specific *experiences*: the hepatitis C diagnosis and the intervention program including counselling and treatment with the prospect of curing the participant's HCV. Below we will discuss how these two experiences impacted the participants' sense-making work.

In line with findings of two other qualitative studies [44, 45], we noted that the first experience of hepatitis C diagnosis was usually unexpected and often a shock. The diagnosis led to reflection, leading to individual explanatory patterns regarding transmission and consequences for sexual behavior. However, as described in previous studies [44, 45], the behavioral change resulting from such reflection, varied between study participants. Across the mentioned studies, some MSM reacted to their diagnosis by taking a sexual break or reducing sexual risk behavior, whereas others showed little or no behavior change.

The second important experience inherent in the constitutive pattern was the prospect of being cured from HCV after participation in treatment and counselling. Interestingly and in contrast to other studies the prospect of cure also induced negative feelings in participants for different reasons: Whereas some men described feelings of shame toward their physician if a reinfection would occur, others described ambivalent feelings toward the burden of having to look again. To our knowledge, this is the first time that negative aspects of HCV cure in the perceptions of MSM have been addressed and highlights a contrast to a study result during the era of Interferon-based therapy in which all interviewed HIV-infected MSM after cure spoke completely positively about their HCV-free status [46].

Alongside our constitutive theme, based on the results of the participants' sense-making work, we divided them into three groups: *1) Avoid risks: get rid of hepatitis C for life; 2) Minimize risks: live as long as possible without hepatitis C; and 3) Accept risks: live with*

the risk of hepatitis C (see fig. 1). A meaningful difference was observed in the experience with DAA on the men's perception of HCV severity and susceptibility of reinfection. Interestingly this changed outcome expectation (from serious HCV infection to treatable) might explain the differences in the likelihood of behavior changes [40]. This could explain why men who perceived HCV infection as a major problem chose the *Avoid risks* sense-making strategy, i.e., were most committed to behavioral change. This group showed an additional difference compared to the two others. These men had already initiated behavior change in between study screening/inclusion and the start of the behavioral intervention. According to the stages of change defined in the TTM, this group seemed to be in the phase of "acting". Hence, they used the behavioral intervention to work on maintaining and sustaining the changes they had made [41]. In contrast, MSM with the sense-making *Accept risks* were particularly attracted by the DAA which they weighed against the perceived difficulty of behavior change, leaving them more open to re-treatment. This suggests that men were also influenced by the perception of treatment burden. Lambers et al. [46] described the same but in reverse. In their study, the perceived burden of Interferon-treatment was high and resulted in a motivation for behavior change to avoid reinfection. Our finding suggests an impact of an easy experienced treatment on less motivation for behavior change in some men, a concern also formulated by Lambers et al. [46].

More variation in response to the intervention program was in MSM using the sense-making of *Minimize risks*. They responded to the counselling with reflection about risk behavior and this led the men to prepare or even implement behavioral changes as intended with motivational interviewing techniques [47]. Within TTM [41] this corresponds to they are in the phase of preparation or action. However participants in our study also described their challenges with behavior change, because change of certain behaviors were non-negotiable for them (e.g., condom use), whereas others were perceived as feasible (e.g., fisting with gloves, not sharing lubricant). This finding is consistent with Bandura's concept of self-efficacy [40], i.e., the principle that a person's perceived capability to perform a certain behavior influences their decision for or against a change that depends on that behavior.

Our study setting presented specific challenges for the evaluation of the behavioral intervention. First, the Swiss HCVree Trial ran in a real-world context with the goal of micro-elimination in the population of MSM with HIV/HCV co-infection, which rendered a controlled trial design impossible. Second, since to our knowledge no HCV specific intervention had been developed for this population, we have implemented an intervention

systematically adapted from an HIV sexual risk reduction program [48]. Given these two aspects, we put priority on the qualitative post-intervention evaluation, focusing on participants' responses to—and particularly their acceptance of—the intervention, then of what changes it led to and why [49-51]. Despite the fact that interviews were conducted 6 to 12 months post-intervention, participants stories reflected rich and meaningful experiences with and around the intervention well remembered. Given the research question to better understand the men's response to the intervention, we had to focus on how experiences unfold over time. Although we did not use a trajectory approach as described by Grossoehme [52], we used a similar approach in the analysis. We first identified themes and then further investigated them in terms of how they changed over time. This suggests that post-intervention evaluation could provide meaningful results and a longitudinal design might not always be mandatory.

This study includes limitations. First, the purposeful sampling strategy we used instead of interviewing all 51 intervention participants, worked well regarding individual characteristics (e.g. age distribution, years since HIV or HCV diagnosis). However we did not reach maximum variation in centers as we were not able to recruit participants from Switzerland's French speaking region. Therefore, our results fail to represent one region. However, findings present a variety of responses to the complex intervention program (behavioral counselling and DAA) sufficient to support not only a subsequent mixed-methods quantitative outcome evaluation, but also the advancement and tailoring of an intervention program focusing on HCV micro-elimination to participants' needs. Overall, we can derive first implications for further intervention development and clinical practice. It seems to be essential to keep in mind that both, the behavioral intervention and DAA-treatment, have an influence on future behavioral changes. Furthermore, in accordance with others, we describe that the HCV diagnosis as such may lead to reflection and sometimes behavioral changes [44]. This indicates that the timepoint of diagnosis could be teachable, indicating participants openness for information and reflection, that could be used for motivational support by clinicians [53, 54]. Additionally, the three groups describing different sense-making with the intervention supports further intervention tailoring in respect to content, duration and timing. For example, by shortening the behavioral intervention for the group of *Avoid risks* with a strong focus on reassurance to increase maintenance of behavioral change or by extending the behavioral intervention for the group of men who report sexualized drug use behavior with a stronger focus on this management to overcome ambivalence and initiate change for safer use.

Conclusion

This study used an inductive interpretative approach to explore men's sense-making premises and strategies regarding a complex behavioral intervention, helping us both to understand the intervention's meaning for participants sexual risk decision making and to explain the diversity of their intervention' responses. The constitutive theme highlights the influence of participants' pre-existing attitudes on their coping with HCV infection, their motivation towards joining the HCVree program and, most importantly, their future actions following it. The results will facilitate ongoing development of this and similar programs' behavioral interventions, particularly by identifying intervention components that can be tailored to fit each key group's attitudes/beliefs to reach an optimal impact.

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Chapter 6. Exploring the impact of a sexual risk reduction intervention to prevent hepatitis C re-infection in HIV-infected MSM: A mixed-methods study

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6.1 Abstract

HIV-infected men-who-have-sex-with-men (MSM) cured of hepatitis C virus (HCV) show high levels of HCV re-infection. Within the Swiss HCVree Trial, HCV treatment was offered alongside a sexual risk reduction intervention. In a participant subsample, a qualitative evaluation identified three sense-making work groups. Testing the hypothesis that the three groups also differ regarding goal-setting and sexual behavior post-intervention, we now conducted a convergent mixed-methods study.

A qualitative analysis indicated seven domains reflecting broader risk reduction strategies; quantitative analysis largely supported differentiation of the groups; and qualitative-quantitative data merging validated three group hypotheses.

One group predominantly shared the goal of using condoms consistently; these men increased their condom use with non-steady partners. Groups two and three showed broader approaches: e.g., planning for safer dating or preparing and using tools to reduce blood exposure, but no change in condom use with non-steady partners. The majority of participants reported sexualized use of stimulant drugs, but no change was seen post-intervention.

Our results improve our understanding of the heterogeneity of intervention responses/outcomes and inform further intervention development. They also underscore the need for outcome variables/questionnaire items that more accurately reflect the diversity of risk reduction strategies.

Trial registration number: NCT02785666

Keywords: Homosexuality, Male; hepatitis C; HIV Infections; Sex Counselling; Harm Reduction

6.2 Background

Despite the availability and broad implementation of highly-effective hepatitis C virus (HCV) treatment for several years, post-treatment HCV re-infection rates in HIV-diagnosed men-who-have-sex-with-men (MSM) are high. This highlights a public health challenge and emphasizes the need for combined hepatitis C prevention strategies that include interventions to reduce sexual and drug-use-related exposure [1-4].

Sexual HCV transmission plays a major role for re-infection, with several associated risk behaviors, e.g., condomless anal intercourse, receptive fisting, group sex, sexualized drug use (SDU), and especially injection drug use (IDU) [3, 5-8]. While sound evidence supports sexual risk reduction interventions for HIV prevention, what little exists for HCV prevention is based mainly on clinical programs.

In 2016/17, the Swiss HCVree Trial tested a multi-component HCV prevention package. HIV/HCV co-infected MSM participating in the Swiss HIV Cohort Study (SHCS) [9] received direct-acting antivirals (DAA) at no charge. Those who reported condomless anal intercourse with non-steady partners (nsCAI) over the previous year were additionally invited to participate in a newly developed HCV risk reduction intervention [10]. Participants received four individual counseling sessions, delivered by specially-trained nurses. The first session focused on exploring the participant's emotions and values regarding their sexuality and drug use, the second on perceived benefits/disadvantages of their current sexual behavior, the third on individual goal-setting for behavior change congruent with their preferences and their confidence that they could achieve those goals, and the fourth on goal implementation and reinforcement [11].

Accurate evaluation of this feasibility test was vital. A qualitative study exploring the intervention's meaning to participants [12] identified three diverse work of sense-making regarding the study program: 1) Avoid risks: get rid of HCV for life; 2) Minimize risks: live as long as possible without HCV; and 3) Accept risks: live with the risk of HCV. These sense-making works reflected differences in how MSM experienced living with their HCV infection, how they experienced DAA treatment, how they used the intervention, and how they dealt with their vulnerability to re-infection after being cured (table 1).

Table 1: Short description of the three groups of sense-making work

No	Sense-making work	Description
1	Avoid risks: get rid of HCV	• HCV is serious, being cured by DAA is a unique opportunity • Behavioral change initiated prior to the intervention • Intervention helped to maintain behavioral changes • Re-infection must be prevented
2	Minimize risks: live as long as possible without HCV	• HCV is a problem but manageable via DAA • No thoughts about behavioral changes prior to the intervention • Intervention helped them learn about behavioral changes and to decide what was feasible • Re-infection might happen but could be treated again
3	Accept risks: live with the risk of HCV	• HCV is socially limiting but manageable via DAA • In men's view, feasible behavioral changes had already been implemented prior to the intervention • Intervention helped to reflect on the difficulties of other behavioral changes • Re-infection will happen, but re-treatment is easy

These qualitatively generated sense-making groups might be very useful to inform further intervention development and tailoring. We assumed that the three groups also differed regarding a) the content of sexual risk reduction goals set in the third intervention session; b) the extent of their nsCAI, SDU, and IDU at t0 and t6; and c) their age and medical history. These assumptions prompted the following three hypotheses:

- Group 1: Clear and firm behavioral goals; low levels of nsCAI and SDU at t0 maintained at t6
- Group 2: Far-reaching and diverse behavioral goals; high levels of nsCAI and SDU at t0, lower levels of SDU at t6
- Group 3: Few behavioral goals; high levels of nsCAI and SDU at t0 and t6

To validate these hypotheses, we applied a mixed-method approach, bringing together the strengths of qualitative and quantitative data [13]. Via a qualitative thematic analysis, we described domain summaries of participants' individual HCV risk reduction goal setting during the intervention. In parallel, a quantitative pre/post analysis of intervention outcomes was conducted. We then compared the three groups regarding age, medical history, the extent of nsCAI, SDU, and IDU at t0 and t6 and each group's goal-setting domains to validate the qualitatively generated groups against how their members used the intervention.

6.3 Methods

A convergent mixed-methods approach was used, a type of design for which qualitative and quantitative data are collected concurrently, analyzed separately, then merged for comparison [14] (see figure 1).

For this study, we used qualitative and quantitative data from MSM who were enrolled in the Swiss HCVree Trial [10] and had participated in both interventions, i.e., DAA medical treatment; and sexual risk reduction counseling (n=51). We obtained ethical approval from the relevant cantonal ethics committees for all seven study sites and written informed consent from all study participants.

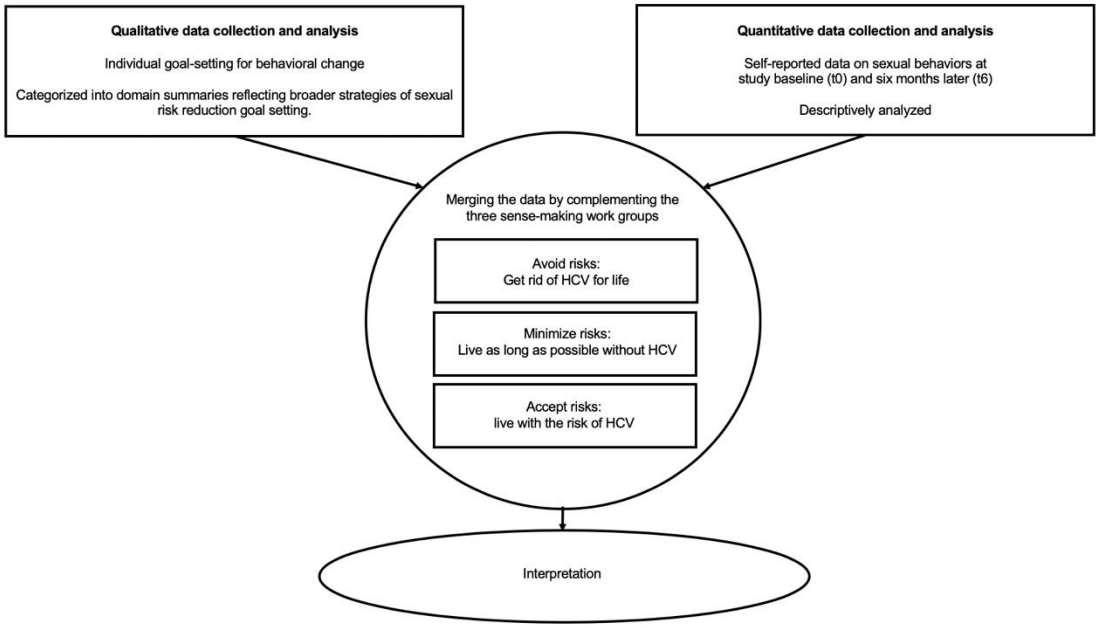

Figure 1. Study diagram for the convergent design

Qualitative data collection and analysis

For this study, we used the behavior change goals participants set individually in their third counseling session. Each had set himself at least one goal he felt motivated to achieve. He also defined the activities necessary to achieve his goal [15]. The written goals were copied after the session, with the original given to the participant and a copy kept with the study documents.

All available forms with hand-written goals were analyzed using a coding reliability thematic analysis approach [16]. Our aim was to better understand goal-setting by

systematically categorizing individual goals into domain summaries reflecting broader strategies of sexual risk reduction goal-setting. In order to facilitate comparison of inter-group differences, we counted the individual goals within each domain.

Quantitative data collection and analysis

Every participant received a sexual and drug use behavior questionnaire to self-complete at the start of DAA treatment and counseling (t0) and again six months later (t6), *i.e.,* three months after termination of DAA treatment and counseling. Items asked about anal intercourse with non-steady partners, condom use, fisting, use of stimulant drugs (cocaine, methamphetamine, ketamine, or mephedrone), SDU (use of γ-butyrolactone/γ-hydroxybutyric acid [GHB/GBL], cocaine, methamphetamine, ketamine, or mephedrone during sex), and IDU in the last 6 months (yes/no). Additionally, participants completed two validated questionnaires: Attitudes towards condom use were measured via 13 items using a 5-point Likert scale (1 = “I don’t agree” to 5= “I completely agree”) [17]; condom use self-efficacy was measured via five items on a 10-point visual scale (0= “I cannot”; 10= “I am sure that I can”) [18]. Socio-demographics and clinical data were assessed using the standard SHCS/clinical records questionnaire.

Available data were descriptively analyzed using medians (and interquartile ranges (IQRs)) for non-normally distributed data and frequencies (percentages) for categorical data and pre-post analyzed outcomes, i.e., nsCAI, fisting, use of stimulant drugs, SDU and IDU. We used Chi-square tests for categorical and Mann-Whitney U tests for continuous variables.

Data integration

After separate analysis of each data set, we integrated the results by merging the data for comparison [19]. In order to validate the three study hypotheses, we focused on the subsample of men (n=17) who had participated in the qualitative evaluation that generated the three sense-making groups. After examining the comparability of these interview participants (who had been purposively sampled to achieve maximum variation [20]) against those who had not been interviewed (n=33), we complemented the three groups with all available results–socio-demographic characteristics, sexual behavior, drug use behavior, results of psychosocial constructs and goal-setting– and validated the three generated hypotheses.

6.4 Results

Qualitative results—Strategies for sexual risk reduction

Individual goals were provided by 47 (92%) participants. These were categorized into seven domain summaries reflecting broader strategies of sexual risk reduction goal setting: 1) *planning for safer dating*; 2) *preparing and using tools to reduce blood exposure;* 3) *improving my social and personal life; 4) using condoms consistently; 5) disclosing HCV to my sexual partners*; 6) *reducing sexualized drug use; 7) other* as described in table 2. Two participants (4%) had set a single goal, 21 (45%) two goals and 24 (51%) three goals, resulting in 116 individual goals in total.

Table 2: Seven identified broader HCV risk reduction strategies

Domain summary	**Examples of original quotes to illustrate the meaning**	**n=116 goals in 47 MSM n (%)**
Planning for safer dating	"I leave my mobile phone at home to avoid spontaneous dates through social media." "I leave relevant chatrooms." "We define and implement the rules of the game together in advance of sex."	30 (26)
Preparing and using tools to reduce blood exposure	"I create my personal (happy) box with my toys and lubricant." "I insist my partners take clean gloves when I get fisted." "I organize my personal snorting tubes."	26 (22)
Improving my social and personal life	"I look for sustainable leisure activities at the weekends outside sexual encounters." "I am going to the gym 3–5 times a week for a better body-feeling and loving my body again."	16 (14)
Using condoms consistently	"I will behave safely, meaning take condoms with me and use them with no discussion." "I will have safer sex with occasional partners although oral."	13 (11)
Disclosing HCV to my sexual partners	"I talk with potential sex partners about HCV" "I ask a potential sexual partner if he is HCV positive or negative"	12 (9)
Reducing sexualized drug use	"I say no for drug use" "I will be having sex without hard drugs for one month. "	12 (9)
Other	"I go for regular STI screens." "I regularly read the latest HCV information."	7 (6)

Quantitative results—Representativeness of interviewed MSM

Of the men who received the counseling intervention and DAA, fifty (98%) reported on their sexual and drug use behavior at baseline (t0), and 48 (94%) at t6.

Comparison of baseline data between the 17 MSM interviewed to determine the three groups (table 1) and those not interviewed (n=33) showed no significant differences (table 3).

Table 3. Comparison of socio-demographics, sexual behavior, psychological constructs and goal-setting themes among interviewed and non-interviewed participants

Characteristics	**Non-interviewed n=33**		**Interviewed n=17**		**p[§]**
Socio-demographics					
Age, median (IQR)	44 (34–50)		44 (41–53)		1.000
Skin color white, n (%)	26 (79)		16 (94)		0.646
Post-secondary education, n (%)	15 (45)		8 (47)		1.000
Years since HIV diagnosis, median (IQR)	8.6 (5.9–13.5)		10.9 (6.5–17.3)		0.762
Years since HCV diagnosis, median (IQR)	1.7 (0.7–4.9)		1.6 (1.2–4.1)		0.836
Sexual behavior	**t0**	**t6**	**t0**	**t6**	
Any nsAI	22 (67)		13 (76)		0.946
		19 (58)		13 (76)	0.710
Any nsCAI, n (%)	18 (55)		11 (65)		0.914
		13 (39)		11 (65)	0.468
Any fisting, n (%)	10 (30)		4 (24)		0.952
		9 (27)		4 (24)	1.000
Drug use behavior					
Any stimulant drug use[*], n (%)	20 (61)		11 (65)		1.000
		17 (52)		9 (53)	1.000
Any sexualized drug use[#], n (%)	20 (61)		11 (65)		1.000
		17 (52)		11 (65)	0.825
Any injection drug use, n (%)	10 (30)		2 (12)		0.412
		7 (21)		3 (18)	1.000
Psychological constructs					
Positive attitudes towards condoms, median (IQR)	39 (31–48)		34 (23–39)		0.351
		40 (33–47)		36 (25–41)	0.231
Self-efficacy in condom-use, median (IQR)	28 (20–40)		30 (14–41)		0.963
		28 (25–44)		38 (31–45)	0.28

Individual goal-setting±			
Planning for safer dating	20 (25)	10 (27)	1
Preparing and using tools to reduce blood exposure	18 (23)	8 (22)	1
Improving my social and personal life	9 (11)	7 (19)	0.492
Using condoms consistently	9 (11)	4 (11)	1
Disclosing HCV to my sexual partners	9 (11)	3 (8)	0.892
Reducing sexualized drug use	9 (11)	3 (8)	0.892
Other	5 (6)	2 (7)	1

nsAI, anal intercourse with non-steady partners; nsCAI, condomless anal intercourse with non-steady partners; IQR, interquartile range

§ Chi-square tests for categorical and Mann-Whitney U tests for continuous variables

* stimulant drugs: cocaine, methamphetamine, ketamine, or mephedrone

sexualized drug use: use γ-butyrolactone/γ-hydroxybutyric acid (GHB/GBL), cocaine, methamphetamine, ketamine, or mephedrone during sex

± Multiple goals were possible, every man set between 1 and 3 goals

Mixed-methods results – Validating three hypotheses

The hypothesis for group 1 (clear and firm behavioral goals; low levels of nsCAI and SDU at t0 (maintained at t6)) was confirmed (table 4). This was the only group who set goals in the *using condoms consistently* domain. Importantly, although they had reported nsCAI in the year prior (an inclusion criterion for the counseling segment of the Swiss HCVree Trial), this group's nsCAI levels were already low at baseline. Their scores on self-efficacy and attitudes towards condom use were consistent with these findings—the highest of the three groups. Overall, they also showed the lowest HCV risk profile both at baseline and six months later. However, no change could be measured regarding SDU. These participants had been living for many years with diagnosed HIV (median 20.7 years, IQR 9.2–21.8) and HCV (median 5.8 years, IQR 1.5–9.5).

The hypothesis for group 2 (far-reaching, diverse behavioral goals; high levels of nsCAI and SDU at t0, lower level of SDU at t6) was partly confirmed. Regarding goal-setting, our assumption was correct: they were considering risk reduction in domains other than condom use. MSM of this group showed most activity in the domains of *preparing and using tools to reduce blood exposure* and *planning for safer dating*. This result is well reflected in their unchanged high levels of nsCAI and stable self-efficacy scores at both t0 and t6. The hypothesis that they would show a reduction in SDU at t6 was not confirmed. In contrast to group 1, group 2 MSM had been living with diagnosed HCV for a much shorter time (median 1.6 years, IQR 1.1–2.3).

All components of the hypothesis for group 3 (few behavioral goals; high levels of nsCAI and SDU at t0 and t6) were confirmed. Compared to the other groups, these MSM set fewer goals—and these in the domains of *planning for safer dating* and

disclosing HCV to my sexual partners. Overall, they also showed the highest HCV risk profile both at baseline and six months later. No change could be measured regarding nsCAI or SDU. These men had been living for a rather long time with diagnosed HIV (median 14.7 years, IQR 11.7–16) and HCV (median 1.5 years, IQR 1.2-2); but two of this group's four members had already been re-infected at least once after successful treatment before the trial.

Table 4. Comparing socio-demographics, sexual and drug use behavior, psychological constructs and goal-setting themes across three sense-making groups

	Group 1 Avoid risks: get rid of HCV for life N=5		Group 2 Minimize risks: live as long as possible without HCV N=8		Group 3 Accept risks: live with the risk of HCV N=4	
Socio-demographics, clinical data						
Age, median (IQR)	44 (38–51)		43 (41–52)		49 (42–53)	
Skin color white, n (%)	5 (100)		7 (87.5)		4 (100)	
Post-secondary education, n (%)	5 (100)		2 (25)		2 (50)	
HIV years since diagnosis, median (IQR)	20.7 (9.2-21.8)		9.3 (5.4-11.5)		14.7 (11.7-16)	
HCV years since diagnosis, median (IQR)	5.8 (1.5-9.5)		1.6 (1.1-2.3)		1.5 (1.3-2)	
Treatment for HCV re-infection, n (%)	0		2 (25)		2 (50)	
Sexual behavior	**t0**	**t6**	**t0**	**t6**	**t0**	**t6**
Any nsAI, n (%)	3 (60)	3 (60)	6 (75)	6 (75)	4 (100)	4 (100)
Any nsCAI, n (%)	0	1 (20)	6 (75)	6 (75)	3 (75)	4 (100)
Any Fisting, n (%)	1 (20	0	2 (25)	2 (25)	1 (25)	2 (50)
Drug use behavior						
Any stimulant drug use*, n (%)	1 (20)	2 (40)	3 (37.5)	3 (37.5)	4 (100)	4 (100)
Any sexualized drug use#, n (%)	2 (40)	2 (40)	5 (62.5)	5 (62.5)	4 (100)	4 (100)
Any injection drug use, n (%)	1 (20)	0	1 (12.5)	1 (12.5)	0	2 (50)
Psychosocial constructs						
Self-efficacy condom-use, median (IQR)	39 (38–47)	51 (40-58)	35 (27-37)	36 (30-37)	23 (20-24)	20 (15-22)
Positive attitudes on condoms, median (IQR)	47 (40-47)	45 (38-49)	35 (27-37)	37 (29-41)	10 (7-16)	30 (28-33)
Goal-setting themes‡						
Planning for safer dating, n (%)	1 (20)		6 (75)		3 (75)	
Preparing and using tools to reduce my blood exposure, n (%)	0		7 (87.5)		1 (25)	
Improving my social and personal life, n (%)	3 (60)		3 (37.5)		1 (25)	
Disclosing HCV to my sexual partners, n (%)	1 (20)		0		2 (50)	
Reducing my sexualized drug use, n (%)	1 (20)		1 (12.5)		1 (25)	
Using condoms consistently[b], n (%)	4 (80)		0		0	
Others, n (%)	0		1 (12.5)		1 (25)	

nsAI, anal intercourse with non-steady partners; nsCAI, condomless anal intercourse with non-steady partners; IQR, interquartile range

*stimulant drugs: cocaine, methamphetamine, ketamine, or mephedrone

#sexualized drug use: sexualized use of γ-butyrolactone/γ-hydroxybutyric acid (GHB/GBL), cocaine, methamphetamine, ketamine, or mephedrone

‡Multiple themes were possible, every man set between 1 and 3 goals

[b]One participant took a sexual break, i.e. he had no sex with steady or non-steady partners in the previous 6 months

6.5 Discussion

This mixed-methods study explored the impact of one of the first sexual risk reduction interventions to focus on hepatitis C re-infection in HIV-infected MSM. Our findings confirmed the hypothesis that the qualitatively generated groups regarding participants' sense-making would differ in two ways: a) sexual risk reduction goal-setting during the intervention; and b) behavior change outcomes post-intervention. Overall, these results improve our understanding of the heterogeneity observed in intervention responses and outcomes.

The hypothesis for group 1, that participants have set clear and firm behavioral goals, was confirmed. Interestingly, these were the only group working with goals in the domain of *using condoms consistently*. This was congruent with their pre-post behavior change outcomes, which included low nsCAI reports and a lower risk profile regarding other HCV exposure, *e.g.,* receptive fisting or SDU.

These results emphasize the importance of condom use as a protective behavior. This particular group contradicts the results of two European cohort studies showing a decreasing popularity of condom use in HIV-infected MSM in recent years [21, 22]. However, the observation that these participants had been infected longest with both HIV and HCV with no successful HCV treatment cannot be answered at present. Importantly, these MSM had already decided to change their behavior before the sexual risk reduction counseling started. This unexpected result is supported by their high scores (the highest of the three groups, including at baseline) regarding self-efficacy to negotiate condom use and positive condom attitudes—one or both of which may exert a mediating effect on behavior change as identified by Nöstlinger et al. [23].

The hypothesis for group 2 was confirmed regarding goal-setting and pre-post measurement of nsCAI, but not on decreased SDU at t6. A large majority of this group had chosen at least one goal in the domain of *preparing and using tools to reduce blood exposure*. This result indicates that MSM need effective risk reduction strategies beyond condom use. Such strategies were our intervention program's choice, as the eHealth tool and counseling both included reflection on personal sexual practices in respect to blood and mucosal trauma. This is based on the broader concept of "blood awareness" as a means of reducing HCV transmission [7, 24]. Unfortunately, we did not include outcomes that focused on behavior change by avoiding blood contact and reducing the risk of bleeding. Further revision and development of outcome measures are clearly necessary.

The group 3 participants showed less dedicated goal-setting and no post-intervention behavioral change. Interestingly, this group's goal-setting activities predominantly took

place in the domain of *planning for safer dating*, e.g., “Have no sex with men I don't know” or “Leave my mobile phone at home to avoid spontaneous dates through social media.” These study participants evidently perceive that some types of sexual dating are more risky than others.

This was also reflected in their goals which focused on *planning for safer dating,* including their dealings with geosocial networking applications—a finding congruent with a study observing higher-risk behaviors among MSM using the Internet for dating; [25] however, a more recent cross-sectional study could identify no association between using apps for dating and STI outcomes [26]. Still, our result emphasizes the popularity of dating via apps and the challenges MSM face when using them.

Sexualized drug use was both common and persistent across all three groups. Whereas every group included one participant who set himself a goal within the domain of *reducing sexualized drug use,* only one significant change (in injection drug use) was observed at the three-month post-intervention measurement.

A recent systematic review found a 3-29% prevalence of chemsex in MSM from high-income countries [27]. In Switzerland, several studies have indicated that roughly 10% of MSM regularly engage in SDU [28]. For HIV-diagnosed MSM, though, the *SHCS* showed an SDU prevalence of 13.8% [29]. The much higher levels of SDU in HCV-coinfected MSM suggest a strong association between SDU and HCV infection. However, they may also result from underreporting in the clinical interview setting used by the SHCS, which is more prone to social acceptability bias than the self-completed forms we used [30].

SDU comprises a wide range of risks, not only regarding mental health and addiction, their involvement in prolonging sexual sessions—and therefore STI risk—and their impairment of caution, but also direct risks of blood-borne infection via shared snorting or injection paraphernalia; therefore, harm reduction is particularly important in this group [5, 31-34]. As noted above, though, our one statistically significant improvement regarding SDU related to injection drugs: whereas 34% of participants reported injecting drug use at t0, that number had decreased to 5% at t6 ($p=0.045$). This highlights the importance of integrating “blood awareness” into the counseling intervention.

Since our final data collection, two studies have reported that, as MSM feel under-addressed by traditional harm reduction interventions, they prefer to seek support in familiar sexual health clinics rather than specialized drug services [35, 36]. As our study took place in HIV-specific clinics, this discomfort was not an issue; and the results indicate

that the intervention's on drug-use content worked. However, it remains unclear whether our participants underreported their IDU, as it is a heavily stigmatized behavior.

Overall, our convergent mixed-method approach both complemented and explained our qualitatively identified sense-making work groups by allowing us to validate our hypotheses with both qualitative and quantitative data. Merging the data provided new insights into the intervention's impact and emphasized the inter-group differences. While group 1 focused almost exclusively on condom use and showed measurable behavioral change, both of the other groups relied mainly on *blood awareness* and safer dating; however, these activities effects on broader risk reduction strategies were not measurable.

Overall, our results emphasize the importance of a counseling intervention that addresses a broad range of HCV-related behavioral and contextual risk factors rather than focusing exclusively on condom use. They will allow us to further develop, individualize and tailor the *HCVree and me* intervention to accommodate the needs of our dynamic target context [37].

This study has certain limitations that warrant mention. For example, all of our results were based on rather small samples. However, the combined use of quantitative and qualitative data allowed us to identify three distinct sense-making groups, which led to consistent findings. Our results also identified weaknesses in the current questionnaire design—especially regarding "blood awareness" and related behaviors—implying a need to implement a range of items reflecting the broad range of HCV exposure- and/or risk-reduction strategies.

Conclusion

By reflecting differences in individual goal-setting and post-intervention behavioral changes, this mixed-methods study validated our three qualitatively generated sense-making groups. These findings suggest that groupings based on sense-making work can be used to inform further intervention development, particularly by group-specific tailoring of intervention content and duration and via the use of additional outcomes. Most importantly, across all three groups SDU-specific content clearly needs improvement.

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Chapter 7. Discussion

This final chapter summarizes and discusses the key results of the four articles included above. This is followed by a discussion of methodological strengths and limitations as well as implications for research and clinical practice.

7.1 Key results

In the first phase of this research, we applied the concept of scaling-out, further developing an evidence-based intervention (EBI) from a context of HIV prevention to one of HCV prevention. In order to identify, develop and implement the required adaptations, we used the widely-used IM Adapt framework [1].

During the process, we identified certain limitations inherent in this approach. For example, dealing with the changing context of HCV prevention in HIV/HCV co-infected men was particularly challenging (e.g., selected EBI was developed before the Swiss Statement in 2008). Therefore, we decided to integrate an additional contextual analysis using a participatory approach. This innovative combination of methods enabled a successful scale-out, at the end of which the adapted intervention, now named *HCVree and me*, was available for the Swiss HCVree Trial. In this situation, thinking concurrently in terms of several concepts and combining diverse methods seemed to be a factor for success **(chapter 3)**.

The *HCVree and me* counselling intervention was embedded in the Swiss HCVree Trial for HIV/HCV co-infected MSM who had reported inconsistent condom use with non-steady partners over the previous year (nsCAI). In parallel, all participants received the same highly-effective HCV drug therapy. With the combined biomedical/behavioral intervention we pursued a comprehensive prevention approach. The aim was to reduce HCV reinfections by reducing sexual risk behavior, thereby sustaining the long-term effect of the medical therapy.

The subsequent evaluation showed that the participants responded in different ways to these interventions. With the constitutive theme of *Giving Hepatitis C a place and letting it go again,* we were able to show that all participants entered the behavioral intervention influenced by their previous experiences of living with a chronic HCV infection.

Additionally, the participants responded differently to the idea of pairing a behavioral intervention with effective HCV therapy. We succeeded in preserving the diversity in the qualitative responses by grouping men based on their sense-making work: *Avoid risks: get rid of hepatitis C for life*; *Minimize risks: live as long as possible without hepatitis C* and *Accept risks: live with the risk of hepatitis C.* This level of diversity is a strong basis for further development of tailored interventions **(chapter 5)**.

Another important evaluation result concerns the question of the inclusion criterion's sensitivity. We asked men who had reported nsCAI for the previous year to participate in the behavioral intervention. Our baseline data analysis showed that this behavior was quite predictive of further HCV relevant risk behaviors. At the same time, our analysis showed that sexualized drug use (SDU) was prevalent (37%) and that using nsCAI as an inclusion criterion neglected the subgroup of men with this very significant risk behavior (18%) **(chapter 4)**.

In our mixed-method analysis, we complemented the sense-making groups' data with qualitatively described domains of participants' individual sexual risk reduction-goals and those of the quantitatively pre-post-analysis of self-reported sexual behavior. Merging the various data allowed us to present intergroup differences in relation to specific behaviors and activities. This result both confirms the groups' relevance and serves as an important basis for further HCV prevention in HIV-infected MSM **(chapter 6)**.

Overall, our evaluation of sexual risk behavior confirmed the increasing international trend of SDU in this sub-population. We received even higher reports from our behavioral counselling intervention participants (60% reported SDU and 24% injecting drugs at study baseline). And after six months, despite the behavioral counselling intervention, no change could be measured.

Such a high self-reported prevalence of SDU in our study group emphasizes the growing importance of this behavior, which is associated with significantly increased transmission risk. It also highlights the need for behavioral counselling interventions focusing strongly on this specific behavior.

Based on these findings, we also recognized the urgent need for an improved outcome measurement. Considering that this study's changes were too small to measure, future iterations will need to apply an instrument reliable and sensitive enough both to measure safe SDU levels and to show changes—even very small ones—after an intervention.

7.2 Scaling-out and the need for combined approaches

We took the opportunity to scale out an EBI rather than developing a completely new one. We chose this approach not only to save resources—it is efficient in terms both of time and of personnel—but also to reuse already developed evidence and make it available to a broader group.

Considering that it often takes many years for results of RCTs to be integrated into practice (if ever), i.e., research incurs huge resource costs with little if any benefit to public

health [2, 3], it is becoming increasingly important to build up evidence that can be gradually but quickly incorporated into practice. In recent years, therefore, methodological approaches have emerged to accelerate implementation. Scaling-out is one such approach [4].

One prerequisite for scaling-out is the availability of an EBI [4]. With the "computer-assisted intervention for safer sex" (*CISS*) we were able to build on a theory-based intervention that had been successfully tested via an RCT in a similar setting [5, 6]. To use *CISS* we had to scale it out for use in a subgroup of HIV-infected MSM participating in the Swiss HCVree Trial. Using a step-wise approach, we identified differences not only between this subgroup and the overall population of MSM but also between our intended setting and that of the original intervention. These steps made it clear that, in addition to content, broad contextual adaptations would be necessary.

This finding is consistent with two reviews on adaptation, both of which describe content and contextual adaptations as those most frequently performed [7, 8]. Within the framework for the classification of EBI adaptations, however, three of the four described contextual adaptations refer to the setting, format and personnel; only one refers to population differences [9].

One reason for this lack of focus on the target population is that, until a few years ago, context was discussed mainly in terms of an intervention's implementation in "real-world" settings. For that purpose, the dominant tactic to determine best implementation strategies was to identify barriers and facilitators in the setting [10].

For the *HCVree and me* intervention, we focused on differences in the current sociocultural context. To better decide on adaptations, we combined a traditional intervention development approach—IM Adapt—with an implementation research-based contextual analysis. Using a framework developed by Chaudoir et al. [11], we conducted a structured multi-level assessment of contextual factors.

Also in line with implementation research, we chose a participatory approach, which made use of expert input from multiple stakeholders. As Movsisyan et al.'s systematic review of adaptation studies [7] shows, while other projects have involved stakeholders, they have followed no underlying conceptual framework to guide that involvement. We enlisted our stakeholders' expertise twice: first for data collection and second to support the process of making adaptation decisions [12, 13].

Our combined approach both facilitated and necessitated extensive adaptations to content and context. Recent high-impact publications on the transferability of interventions into new contexts also helped us understand the complexity of our task.

While newer frameworks such as *Context and Implementation of Complex Interventions framework* (CICI) facilitate the systematic investigation of contextual factors [14], all leave a number of very significant questions open. For example, on what common basis should decisions on contextual adaptation be made; and will comprehensive re-evaluations of adapted EBIs become necessary as a result [15]?

The dissertation contributes substantially to this discussion. Among its most important benefits to future researchers is its illustration of how a contextual analysis can help uncover contextual changes and determine when and in which ways to incorporate stakeholder input into the adaptation process.

7.3 Responses to the behavioral intervention

In this work, we strongly emphasized our qualitative evaluation of participant responses to the *HCVree and me* behavioral counselling intervention. Although the participants were selected according to a single risk behavior (nsCAI) and received the same theory-based behavioral intervention, we noted significant diversity in their responses. This variation led us to group the respondents based on their sense-making work.
The diversity resulted from a variety of experiences, several of which we could determine. One important was the men's experience of two interventions—one behavioral, one biomedical—in parallel. Regarding the two interventions' mutual influence, we immediately noted the difficulty of evaluating a comprehensive prevention strategy in relation to its individual components [16]. However, in our case, this finding emphasizes that there *was* an interaction between treatment experience and behavior. As a key result of this research, this is first qualitatively described and later confirmed in the results of the mixed-methods study.

Depending on the sense-making work groups, the interaction between the curative therapy and the behavioral intervention had a number of implications. For the men whose sense-making work fit the *Avoid risks: get rid of hepatitis C for life* group, DAA therapy offered a unique chance to be cured of hepatitis C. In contrast, those whose sense-making suggested *Minimize risks: live as long as possible without hepatitis C, or even more so, Accept risks: live with the risk of hepatitis C,* found the medical therapy an effective and, if necessary, easily repeated intervention.

This result emphasizes an important effect of treatment on behavior, i.e., that, for many recipients of DAA treatment, it is experienced as simple. This stands in sharp contrast to the earlier Interferon-based therapies, the experienced burden-some treatment led to an increased motivation to reduce risk behaviors after successful treatment [17]. Further, two qualitative studies among users of pre-exposure prophylaxis (PrEP) also showed different handling of personal risk behavior after receiving PrEP. Some MSM adopted behavior that entailed a higher risk of contracting other STIs; others did not. However, all agreed that PrEP led to a feeling of increased safety and security—a normal and desirable emotional response to an effective biomedical intervention [18, 19].

Whether the availability of DAA therapy has led to higher-risk sexual behavior is difficult to answer at present. Regardless of our participants' sense-making work, all described their cure as a relief.

This response is in line with those of 20 participants in a qualitative study in Australia. Following successful HCV therapy, as they no longer had to worry about their health and felt "normal" again, they also reported feelings of relief.

Still, some acknowledged the possibility of HCV reinfection as a new burden with potential for a new stigma. Regardless of social concerns, Richmond et al. [20] emphasized the importance of care—regarding both prevention and the potential need to repeat treatment—during the follow-up period.

We agree with this statement. However, we also emphasize the strong possibility that reinfection will carry a stigma. In our research, there were clear indications of the danger inherent in such an outcome. For example, one man spoke of a reinfection as a *disgrace*; others noted that a cure was negatively perceived because they now felt it was their duty to avoid reinfection.

The stigma attached to HIV, which has been well-studied, often leads to discrimination, hinders access to health care, increases stress and results in negative health outcomes [21, 22]. Regarding HCV, a concept analysis suggested comparable results [23]. To overcome or reduce this stigma, Treloar et al. [24] emphasized the importance of a good relationship with the health care provider (HCP).

In HIV-infected MSM, such a stigma is further relevant because it is a barrier to HCV disclosure [25]. Our results indicate that a reinfection-related stigma appears to be an issue not only among drug users but also among MSM. As this issue may be relevant to HCV prevention, it requires further investigation.

Regarding the constitutive theme *Giving Hepatitis C a place and letting it go again,* the positive experiences with the behavioral intervention were evident. All participants felt

personally addressed by the free choice of themes that interested them. Several described using the counsellor as a neutral partner for discussions about their challenges and emotions, not necessarily focusing exclusively on HCV infection and sexual risk behavior.

This result shows clearly that the chosen theoretical framework was appropriate, e.g., the focus of the first session was precisely focused on exploring emotions and values, supported by video clips and motivational interviewing techniques [26, 27]. The result is important in that it emphasizes a key intervention component, indicating that it should be maintained even as it evolves.

The same need for emotional and social support was a central theme of a 2012 qualitative study of HIV-positive MSM. Vanable et al. [28] observed that the search for personal support was a high motivation of HIV-infected MSM to participate in a behavioral intervention.

The importance of encouraging conversations is further emphasized in another qualitative study of MSM under PrEP. Its results showed that changes in sexual risk behavior are dependent on numerous surrounding psychosocial factors [18]. Therefore, the importance of counselling in parallel to PrEP—especially in such a complex setting—is discussed [29, 30]. As our experience in the Swiss HCVree Trial confirms, both initiation and treatment phases can provide excellent environments for high-quality counselling.

In the tested *HCVree and me* intervention, we used content-driven tailoring [31]. Participants could choose themes in the eHealth tool according to their needs or preferences. This was additionally supported by motivational interviewing and based on the underlying theoretical model [26, 27]. But the diversity in sense-making work showed that, despite our groups' enjoyment of the discussion, the need for the content or lengths of the discussion varied. This is a valuable finding. Similar results of a formative evaluation allowed Pleasant et al. [32] to successfully tailor an EBI for use in a new location and culture.

Analogous to these experiences, in our context one can consider what behavioral adaptation needs prevailed in our three sense-making groups and use these as a basis for further tailoring. This could go beyond the already integrated content-based tailoring, leading, for example, to logistical tailoring, i.e., adjusting the length of the intervention or dose to needs of each sense-making group.

Similar tailoring might also be interesting for the development of effective digital behavioral interventions, which are currently gaining in popularity. A recent systematic review of eHealth prevention interventions aimed at MSMs showed a positive short-term effect

on behavioral changes [33]. Our qualitative results could offer guidance for researchers working to extend their tailoring with the aim of integrating the views of more response groups and improving their outcomes.

7.4 Dynamics in sexual risk behaviors

Within our group of HIV-infected MSM, sexual risk behavior is extremely dynamic. This research has described several of the forces influencing these men's sexual risk behavior, thus increasing our understanding of future prevention needs and offering tools to help meet those needs. At the same time, our results show the limitations of the current evaluation, as defined measures and instruments were not sufficiently focused on working with such dynamic behavior.

It is well documented that sexual behavior in any group will change over time in response to strong external stimuli. For example, the widespread use of highly effective HIV therapy leads to relatively low-risk condomless sex (regarding HIV transmission) with a serodifferent partner [34]. And the current trend of sexualized drug use (SDU) in MSM is clearly associated with increased HCV transmission risks [35, 36].

Our research confronted us with these and other dynamics from numerous angles. First, we observed rapid changes in condom use between screening and baseline. We had invited men to participate in the behavioral intervention if they had indicated nsCAI in the year prior. However, at baseline only 58% of them reported this behavior—somewhat fewer than the expected 100%. A possible explanation was found in the qualitative data of the group with the sense-making *Avoid risks: get rid of hepatitis C for life.* Even before the intervention started, to enhance the effect of treatment, these men had switched to consistent condom use (with non-steady partners). This course of action stands in contrast to the other two groups, i.e., those whose sense-making work were either *Minimize risks: live as long as possible without hepatitis C* or *Accept risks: live with the risk of hepatitis C.* For these groups, as condoms had clearly lost their importance, they chose other risk reduction strategies.

Similar attitudes were noted in studies that observed a decreasing importance of condoms in HIV-infected MSM [37-40]. They also agree with statements made by our stakeholders during contextual analysis. Clinicians were skeptical that men would be willing to discuss condom use, and HIV/HCV co-infected MSM themselves spoke of condomless sex as a widely accepted norm in their community and therefore a matter of declining influence regarding opinions and related behaviors.

On the one hand, such responses show how quickly risk-reduction behavior can change, while partly explaining our difficulties in interpreting evaluation results; on the other, they show that, contrary to the skepticism of clinicians, condom use continues to occupy a position as a protective behavior in at least one subgroup of HIV/HCV co-infected MSM.

A similar effect appears to have arisen in a qualitative study of MSM under PrEP. There, one group reported returning to consistent condom use, as STI diagnoses had shown them that PrEP did not protect them against everything [41].

Our evaluation also stresses the challenge of maintaining behavioral change. For example, relapses into old behaviors are to be expected and neither end nor reverse the process [42]. Men who changed to consistent condom use noted that changes in the psycho-social environment could lead to relapses. These observations both offer a likely explanation for certain unexpected behavioral changes and stress the importance of targeting multiple behaviors, including some whose influence appears to be declining, via a single intervention.

While nsCAI behavior certainly acted as a dynamic within our target group, we observed a greater contextual dynamic in SDU—a risk behavior evident in 37% of the men in the overall sample; and of this risk group, 14% had injected drugs.

A 2019 systematic review reports a 3–29% prevalence of SDU in MSM of high-income countries [43]. In Switzerland, using data from the SHCS, Hampel et al. [44] detected an SDU prevalence of 13.8% in HIV-infected MSM, thereby indicating a significant association between SDU, nsCAI and HCV infection in this group.

This very likely explains the high prevalences of SDU and nsCAI in the Swiss HCVree Trial. Congruently, we observed much higher prevalences in the groups of interviewed men who continued to report nsCAI. Their reports indicated high level of SDU at baseline, with no decrease after six months.

These numbers underscore both the increasing relevance of SDU and the need for new or more focused preventive interventions. In addition, our sensitivity analysis of the nsCAI inclusion criterion showed that 18% of respondents were excluded from the behavioral intervention because they reported SDU but not nsCAI. Especially regarding SDU, which involves a whole range of different risks, such as sharing injection material or participating in activities associated with injuries, and considering that SDU allows longer and more intense sex with multiple partners, prevention is even more important in this subgroup [45-49]. Therefore, our evaluation supports keeping a behavioral intervention open to all men reporting risk behaviors. This said, we acknowledge that the full range of these risk behaviors would have to be reflected in the intervention.

Our decision to include SDU as a new main topic of this intervention was based on the fact that, in addition to the literature, our contextual analysis indicated that many MSM felt unprepared for SDU, but were increasingly confronted with it. We aimed to promote safe SDU, e.g., the use of clean injection or snorting paraphernalia. However, the evaluation showed that, although we had measured the frequency of SDU, we had not adequately measured the aspect of safe SDU.

Currently, the challenges identified here are the subject of scientific discussion. Citing a current measurement problem—SDU is unclearly conceptualized, different recall intervals are used and it is unclear in which settings SDU is recorded—Giraudon et al. [50] emphasize the need for accurate, timely surveillance data. While our results support this appraisal, we further emphasize the need for a validated outcome instrument sensitive enough to detect and measure even subtle behavioral changes.

7.5 Strengths and limitations of methods

This research program was guided by the MRC *framework for complex interventions in health* [51]—or, more specifically, by its first two steps: intervention development and feasibility testing. Originally introduced to support the development of new complex interventions this framework has already been further developed to include a process evaluation [52].

To date, adaptations of complex interventions are not integrated in the framework [15]; therefore, using it as an overarching guide, we integrated various flexible methods. For example, for our development phase, we worked with the IM Adapt framework [1], but additionally followed the recommendations of Gupta [12], used a participatory approach to involve stakeholders (both individuals and communities) from the beginning of the process and performed a multi-level contextual analysis [11].

As this dissertation shows, our use of the MRC framework has successfully strengthened our development, testing and planning processes, enabling the successful scaling-out of a complex EBI. Nevertheless, the unexpectedly large number of socio-cultural adaptations that became necessary posed a challenge, especially with regard to decisions for or against them.

In 2018, intending to address the topic of adaptations and strengthen their guidance for dealing within complex social systems, the MRC announced a revision of their framework [15, 53, 54]. As we had already chosen a similar course with our extended methodological approach—using the concept of scaling-out—while confirming our choice, this

announcement signals the MRC's willingness to pursue a novel, innovative and practical approach. We anticipate that the revised framework will be a powerful tool to adapt EBIs to intervention developers' rapidly changing needs [15].

This work was embedded in the Swiss HCVree Trial, one of the first trials to pursue a comprehensive HCV prevention strategy. This innovative approach enabled the inter-professional development of a behavioral counselling intervention and a feasibility test within the frame of a national clinical trial. However, because this study employed a micro-elimination strategy—meaning there was no control group—evaluation and conclusions regarding its effectiveness were only possible via a pre-post design. Therefore, we used the feasibility test to answer additional evaluation questions. The results, which we collected and analyzed via various methods, significantly support the intervention's further development.

One current limitation is that we have not yet answered evaluation questions about implementation. Although we collected, collated and descriptively analyzed the necessary data within this research, we have not yet evaluated it in depth or published them. These data are particularly valuable for both the further development of the intervention and preparation for implementation outside a study setting.

These limits will be addressed in a trial using a hybrid 2 design. Even without an RCT design, the trial will allow the simultaneous testing of a clinical intervention and defined implementation strategies [55]. However, it will also require the revision of the outcome measurement.

Also, high-quality data will depend on reliable and valid instruments. At the time of our initial development and planning, no such instruments were available. Since then, however, new evidence has been found that can be considered for future use.

7.6 Implications for future research

The results reported here reflect our experience with the development and evaluation of a new HCV behavioral counselling intervention in HIV/HCV co-infected MSM. However, phase 2 of the MRC framework has yet to be completed. We will now revise the intervention according to the results of our evaluation and prepare for the next trial.

The aim of the next adaptation is no longer to scale out the intervention but to increase its reach, improve outcome measurement and prepare effectiveness testing [56]. Thus far, our results have clearly shown that SDU is a prominent behavioral factor of HCV

transmission, and optimization will be necessary regarding both content and outcome measurement.

Again following IM Adapt [1], we propose the following research steps. First, a systematic literature review of SDU will be necessary to synthesize the current evidence. Together with the results of the mixed-method study, this will provide the basis to clarify current and further needed performance objectives (POs), as well as their determinants and outcome expectations regarding SDU. This guides content adaptations and facilitates the selection of appropriate instruments to measure the targeted behavioral change.

Much has been published in recent years on the topic of SDU, and on the development of reliable and valid instruments. For example, researchers have systematically developed, pre-tested and reported on their development of the European Men-Who-Have-Sex-With-Men Internet Survey (EMIS-2017) and made this online questionnaire available in multiple languages [57]. Alternatively, instruments used by experts at the well-known 56 Dean Street Clinic for Sexual Health and HIV are freely available [58]. The detailed formulation of POs will make it easier to clarify the fit between a targeted behavior change and instruments to measure any change that occurs.

Our evaluation indicated a need to adapt the *HCVree and me* intervention's delivery and implementation plan as well as its content. Also, on October, 2017, the Swiss Federal Office of Public Health dropped all restrictions on HCV therapy, i.e., all patients can now be treated, regardless of the extent of their liver damage. Therefore, it is now necessary to reconsider not only which MSM will qualify for a behavioral intervention, but also how and in which settings the intervention will be offered.

Again, people enrolled in clinics will be the focus of attention. May [59] recommends that this translational work include as many persons as possible from the beginning in the process. Exploring their views/attitudes towards the intervention, their acceptance and their concerns regarding implementation will facilitate the intervention's adaptation in relation to testing in a clinical setting [60].

One key result was the identification of three diverse sense-making groups. While Beck et al. [61] posit that such findings can signal where tailoring is necessary, our identification of these groups represented the first step in this process. The qualitative differences found in our sense-making work were validated by the mixed-method analysis, whereby certain behavioral changes could be attributed to specific groups. Now, we need to determine clear and appropriate descriptive variables and characteristics representing each group's specific needs. Afterwards, these characteristics can be prospectively assessed and the intervention tailored according to the results [61].

7.7 Implications for clinical practice

Our results indicate that the period from HCV diagnosis through treatment is also an excellent time to integrate a behavioral intervention: throughout this period, our participants were open for discussion. This finding is also valuable for HCPs in clinical practice, as it suggests that care visits can also be used to address sexual risk behavior.

A recent US study showed that when HCV was diagnosed in HIV-infected persons, their clinical appointments were used far more for providing information than for prevention-related counselling and discussion [62]. Such a missed opportunity could easily become a "teachable moment," i.e., a key time for health care professionals to use an external event to stimulate a person to act and to make behavioral changes [63-65].

Traditionally, successful use of a clinical visit as a teachable moment requires three steps: 1) addressing risky behavior and the patient's individual concerns; 2) enabling change-oriented language (change-talk) to motivate the patient to change his behavior; and 3) making an agreement with the patient to change his behavior. However, our experience with the *HCVree and me* intervention showed that it was important to start by exploring participants' emotional responses to individual problems with safer sex. This step created the basis for identifying and discussing individual risk behavior in depth and allowed us to tailor the intervention to participant's needs.

In clinical practice, this means HCPs should initiate risk-related discussions with patients. Taking the initiative is particularly important because evidence shows that MSM tend to welcome proactive addressing of sexual behavior by HCPs [66, 67]. The same principle applies to starting talks about SDU [68].

However, it is also known that many clinicians have difficulty with such conversations [69]. In our study, we worked with experienced nurses who showed an open and collaborative attitude. They also received three hours of training specifically on motivational interviewing techniques. A 2015 systematic review showed that a clinician's attitude and knowledge regarding patient-centered communication (asking open questions, simple and complex mirroring) can positively influence change-talk [70]; and our experience confirms that even three hours of communication training can give HCPs considerable support. However, it is important to note that the nurses additionally worked with an eHealth tool. Together with the participant, they watched video-clips depicting personal stories featuring role models. Our evaluation indicates that this provided a very effective basis for addressing the men emotionally and facilitated discussion. We must therefore consider whether the use of the eHealth tool would also be feasible in clinical practice.

Sometimes, clinical visit time limits are important barriers to discussion. In such cases, a screening instrument, can be used to quickly collect information on the most important sexual risk behavior, then to guide the content of the conversation. For example, Stuart & Weimann [58] used a small number of guiding questions to identify problematic SDU. A positive screening for this risk behavior then led to a structured assessment, which usually then led to the offer of specialized counselling if necessary.

Our baseline data show that 52 (44%) of our 118 participants had used drugs in the previous six months, of which 44 (37%) had used them before and during sex and 17 (14%) reported injecting drug use. Compared to international data on this topic, these data are high [43]. In addition, the proportions of SDU among men in the *Minimize risks: live as long as possible without hepatitis C* and *Accept risks: live with the risk of hepatitis C* sense-making work groups was even higher. Based on these data, clinicians should address the topic of SDU with HIV/HCV co-infected MSM.

Clearly, this can be challenging for HCPs. Recent SHCS research showed that HCPs often had difficulty correctly naming substances used or correctly reflecting the route of administration [44]. Such a knowledge gap probably results from the rapid increase in SDU in recent years and the current lack of a broad-based conceptualization of SDU. Therefore, the broad dissemination of our data will be important both to sensitize HCPs to this risk behavior and to develop SDU training according to their and their patients' needs.

Two recent studies found that MSM preferred to seek support in familiar sexual health clinics rather than in specialized drug services, because they did not feel addressed by traditional harm reduction interventions [68, 71]. As a reason, they reported a perceived lack of knowledge (among drug clinic personnel) about the connection between drugs and sex, as well as the fear of stigmatization and rejection [68].

With HCPs challenged to recognize and address—in their own attitudes and in those of other HCPs—the many stigmas affecting HIV/HCV co-infected MSM, this result highlights yet another barrier to effective treatment. Successful interventions to help patients deal with stigma in healthcare settings emphasize the importance of bringing up the topic of stigma and promoting participatory care-team-based learning [72]. A first step can be to present the various layers of stigma touched on in this research to clinical teams and encourage joint discussion.

7.8 Conclusion

This dissertation contributes to the evidence base regarding the scaling-out of a complex intervention. While, in our case, scaling-out required an innovative and flexible combination of methods, it's central focus—on adapting an existing intervention to our target context—proved tremendously useful. This was especially true in dealing with our complex contextual environment, which demanded the flexibility to incorporate multiple approaches.

Next, it contributes to the understanding of HCV prevention. Following a comprehensive prevention strategy was possible; however, the components strongly influenced each other, leading to a broad range of responses from our participants. The identified diversity can be used to further improve the intervention by informing group-specific tailoring of intervention content and duration and by adding outcomes. This is only possible because we could describe and validate the three sense-making work groups. It also impacts clinical settings where HCPs need to address individual, multiple sexual risks and initiate the process of behavioral change.

Finally, a high proportion of our sample group reported engaging in high-risk sexualized drug use, thereby shedding light on an important prevention need that will require both the development of a targeted behavioral intervention and the definition of adapted outcome measurements.

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APPOINTMENTS AND PROFESSIONAL EXPERIENCE

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2017 – present **Research Assistant**
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2011 – present	**Advanced Practice Nurse Hepatology** Department of Nursing Department of Gastroenterology/Hepatology Cantonal Hospital St. Gallen, Switzerland
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2018	Statistics 3, Multilevel analysis University of Basel
2018	Walking in the Editor's shoes PPHS, University of Basel
2018	"Leading health care by Developing, Implementing and Evaluating Innovations in Service Delivery", Summer School 2018, SPINE, University of Basel
2018	Writing to be Published – Academic Conventions and Style University of Basel
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MEMBERSHIPS AND SCIENTIFIC SOCIETIES

Since 2019	Onkologiepflege Schweiz
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OTHER ACTIVITIES

2019 – ongoing	Member of the EASL Task Force for Nurses and Applied Health professionals
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AWARDS

2020	Award (2nd price) Theodor-Fliedner-Medaille für innovative Pflegepraxis, Kaiserswerther Diakonie, Düsseldorf, Germany Beckmann, S. & **Künzler-Heule, P.** *Die spitalübergreifende Pflegesprechstunde Lebertransplantation.* Practice development project. University Hospital Zurich and Cantonal Hospital St. Gallen.
2019	Poster presentation award (2nd price) for the presentation entitled *Spitalübergreifende APN-Pflegesprechstunde Lebertransplantation: Ein bedürfnisorientiertes Versorgungsangebot.* Fachsymposium Gesundheit 2019, Cantonal Hospital St. Gallen, Switzerland.
2018	Best Oral Presentation award for the presentation entitled *Development and feasibility of a hepatitis C behavioural risk-reduction intervention in HIV-positive men who have sex with men*. SPINE Doctoral Day, 2018, Lausanne, Switzerland.

PUBLICATIONS

Peer reviewed publications

Hampel, B., Kusejko, K., Kouyos, R. D., Boni, J., Flepp, M., Stockle, M., Conen, A., Beguelin, C., **Künzler-Heule, P**.. . . Swiss HIV Cohort Study (2019). Chemsex drugs on the rise: a longitudinal analysis of the Swiss HIV Cohort Study from 2007 to 2017. HIV Med. doi:10.1111/hiv.12821

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Künzler-Heule, P., Semela, D., Müllhaupt, B. & Beckmann, S. *Nurse-led self-management support in liver transplantation across two hospitals.* Annual Meeting of the Swiss Society of Gastroenterology, Swiss Society of Visceral Surgery and Swiss Association of the Study of the Liver. 2017, Lausanne, Switzerland, September 15.

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Künzler-Heule, P., Pfister-Koch, A., Bergamin, I., & Beckmann, S. *Illustrations to support patient counseling before and after liver transplantation.* Annual Meeting of the Swiss Society of Gastroenterology, Swiss Society of Visceral Surgery and Swiss Association of the Study of the Liver. 2019, Interlaken, Switzerland, September 13.-14.

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