On the potential of a short-term intensive intervention to interrupt HCV transmission in HIV-positive men who have sex with men: A mathematical modelling study

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On the potential of a short-term intensive intervention to interrupt HCV transmission in HIV-positive men who have sex with men:

a mathematical modelling study

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Abstract

Increasing access to direct-acting antiviral (DAA)-treatment for hepatitis C virus (HCV) infection and decelerating the rise in high-risk behaviour over the next decade, could curb the HCV epidemic among HIV-positive men-who-have-sex-with-men (MSM). We investigated if similar outcomes would be achieved by short-term intensive interventions like the Swiss-HCVree-trial. We used a HCV-transmission model emulating two 12-months intensive-interventions combining risk-counselling with 1) universal DAA-treatment (pangenotypic intervention) and 2) DAA-treatment for HCV-genotypes 1 and 4 (replicating the Swiss-HCVree-trial). To capture potential changes outside intensive-interventions, we varied time from HCV-infection to treatment in clinical-routine and overall high-risk behavior among HIV-positive MSM. Simulated prevalence dropped from 5.5% in 2016 to ≤2.0% over the intervention period (June/2016-May/2017) with the pangenotypic-intervention, and to ≤3.6% with the Swiss-HCVree-trial. Assuming time to treatment in clinical-routine reflected reimbursement restrictions (METAVIR ≥F2, 16.9 years) and stable high-risk behaviour in the overall MSM population, prevalence in 2025 reached 13.1% without intensive intervention, 11.1% with the pangenotypic intervention and 11.8% with the Swiss-HCVree-trial. If time to treatment in clinical-routine was 2 years, prevalence in 2025 declined to 4.8% without intensive-intervention, to 2.8% with the pangenotypic intervention, and to 3.5% with the Swiss-HCVree-trial. In this scenario, the pangenotypic intervention and the Swiss-HCVree-trial reduced cumulative (2016-2025) treatment episodes by 36% and 24% respectively. Therefore, intensive interventions could reduce future HCV-treatment costs and boost the benefits of long-term efforts to prevent high-risk behaviour and to reduce treatment delay. But if after intensive interventions treatment is deferred until F2, short-term benefits of intensive interventions would dissipate in the long-term.
**Key words**: Men who have sex with men; Hepatitis C virus; HIV; Direct-acting antivirals; treatment as prevention.

**Abbreviations**: HCV, hepatitis C virus; MSM, men who have sex with men; DAA, direct-acting antivirals
INTRODUCTION

Hepatitis C virus (HCV) is increasingly transmitted among HIV-positive men who have sex with men (MSM), engage in high-risk sexual practices and do not identify themselves as intravenous drug users (1-6).

We and others have shown that reductions in high-risk practices associated with HCV transmission combined with widespread use of direct-acting antivirals (DAA)-based HCV treatment could reduce HCV-incidence and prevalence (7, 8). In some countries including Switzerland, universal HCV treatment for HIV-positive MSM is not possible because DAA-based HCV treatment is only reimbursed for patients who reached METAVIR stage F2 or in rare instances, in patients with clear extrahepatic manifestations of HCV disease.

An intensive, short-term intervention (referred to as intensive intervention) that prevents transmission through risk counseling and provides early DAA-based HCV treatment, could help combat the HCV epidemic among HIV-positive MSM. An intervention of this type is ongoing in the Swiss HIV Cohort Study (SHCS) (9): the Swiss-HCVree-trial (NCT02785666). The primary outcomes of this trial are safety and efficacy of the study drugs. Active HCV testing preceded this trial and all patients infected with replicating HCV genotypes 1 or 4 were offered treatment and risk counselling. To what extent intensive interventions like the Swiss-HCVree-trial can influence the epidemic is however uncertain.

In this modelling study, we assessed the potential to interrupt HCV transmission among HCV-positive MSM of the Swiss-HCVree-trial and a similar intensive intervention where all HCV genotypes could be treated. This hypothetical intervention will be referred to as pangenotypic-intervention and aims to provide more generalizable estimates of the potential of such interventions. We projected HCV prevalence, incidence, genotype distribution and cumulative number of treatment episodes without and with such intensive interventions.
Projections assumed different scenarios outside *intensive interventions*. These scenarios included a range of treatment rates in the clinical-routine reflecting regulatory drug restrictions as well as different trends in high-risk behaviour in the overall HIV-positive MSM population.
MATERIALS AND METHODS

The Swiss-HCVree-trial

The Swiss-HCVree-trial is a phase III, multi-center, open-label trial taking place between June 2016 and May 2017 in the SHCS. In preparation for the trial, intensified HCV-PCR based testing of all MSM participating in the cohort took place between October 2015 and May 2016. All patients infected with replicating HCV genotypes 1 or 4 were offered treatment with the study drugs grazoprevir/elbasvir ±ribavirin. The study drugs are prescribed from June 2016 to February 2017 independently of reimbursement restrictions. The Swiss-HCVree-trial is restricted to HCV genotypes 1 or 4 because grazoprevir/elbasvir is not sufficiently active against HCV genotypes 2 and 3 (which account for 12% of all infections (10)). In addition to HCV treatment, enrolled patients who reported inconsistent condom use with occasional partners (a marker for high-risk behaviour) and provided their consent to a behavioural intervention receive a 45-minute sessions of individual risk counseling at weeks 4, 6, 8, and 12.

Mathematical model of an intensive intervention

To simulate the effect of intensive interventions, we extended a previously developed model of HCV transmission among HIV-positive MSM in Switzerland(7). The model uses a system of ordinary differential equations where the population is classified into 24 compartments defined by i) stage of HCV infection (uninfected, infected, and on treatment); ii) HCV genotype (1 or 4 and 2 or 3); iii) risk behaviour (with and without high-risk practices associated with HCV transmission); iv) enrolment in HIV-care; and v) enrolment in the intensive intervention. The model assumes that a fraction of patients reporting condomless anal sex with occasional partners also engage in practices associated with HCV transmission. Model parameters are described in Table 1 and Supplementary Table S1.
Figure 1 qualitatively depicts the redistribution of the population upon introduction and completion of an intensive intervention.

Model parameterization was fully based on estimates previous to the start of the Swiss-HCVree-trial.

Rules inside the intensive interventions

Rules in common between the pangenotypic intervention and the Swiss-HCVree-trial.

The model matches the testing period of the Swiss-HCVree-trial. Enrolled individuals are treated with DAAs for 12 weeks. Because high-risk behaviour is likely to be underreported (11), and risk counselling is not 100% effective (12), the model assumed that intensified risk counselling within the intensive interventions had an effectiveness of 50% i.e., risk counselling led to 50% of patients with high-risk behaviour at enrolment in the intensive interventions to permanently stop this behaviour. Of note, individuals are assumed to become susceptible to reinfection after HCV clearance regardless of ongoing intensive interventions.

Differences between the pangenotypic intervention and the Swiss-HCVree-trial.

HCV-test and treatment takes place in HIV-positive MSM enrolled in HIV-care for simulations with the pangenotypic intervention and in those enrolled in the SHCS for simulations with the Swiss-HCVree-trial. Of note, we estimate that the SHCS includes 84% of all HIV-positive MSM in Switzerland (13) (14). Patients enrolled in the pangenotypic intervention infected with all genotypes are treated within 3 months since the beginning of the intervention. Analogously, In the Swiss-HCVree-trial patients infected with genotypes 1 or 4 are treated within 9 months since the beginning of the trial.
We modelled the following scenarios for patients not enrolled in intensive interventions and for everyone after the completion of the intervention:

**Scenarios outside intensive interventions**

**Treatment in clinical-routine.** We assumed HCV treatment outside intensive interventions or in absence of intensive interventions (Figure 1) to be DAA-based resulting in 95% sustained virological response (SVR) (15). Treatment rates were chosen to reflect the (mean) time from HCV infection to treatment start corresponding to four different scenarios of clinical-routine:

i) mean time from HCV infection to F2 in the METAVIR scale (16.9 years, labeled F2 scenario) (16), reflecting the current reimbursement restriction in Switzerland and other countries; ii) mean time from HCV infection to F1 in the METAVIR scale (8.2 years, labeled F1 scenario)) (16); iii) 2 years; and iv) 1 year.

**High-risk behavior in the overall (HIV-positive MSM) population.** We considered two main scenarios where the fraction of individuals engaging in high-risk practices associated with HCV transmission: 1) remained stable at the value estimated for 2016 (14%, labeled stable high-risk behaviour) or 2) declined continuously to reach a 50% reduction by 2025 (labeled reduced high-risk behaviour).

**Projections on the effect of intensive interventions**

The overall projection period was 2016-2025. Based on the scenarios depicted above, we reported trajectories, short-term (end-of-intervention, i.e., May 2017) and long-term (2025) HCV prevalence, incidence, genotype distribution and cumulative number of treatment episodes.
We undertook independent analyses that assumed i) no intensive intervention; ii) the pangenotypic intervention; and iii) the Swiss-HCVree-trial. We only projected genotype distribution with the Swiss-HCVree-trial (since treatment is subtype-independent in i and ii).

All these projections correspond to HIV-positive MSM living in Switzerland, including those who are not enrolled in HIV-care.

**Projections with the Swiss-HCVree-trial restricted to SHCS participants.** To allow validation of these results with SHCS data in the future, we also reported separate model projections with the Swiss-HCVree-trial restricted to the subset of modelled individuals enrolled in the SHCS.

**Sensitivity analyses**

We undertook three sensitivity analyses for MSM enrolled in the SHCS. These analyses assumed: I) further increase in high-risk behaviour in the overall population; II) larger fraction of HCV infections acquired by contacts outside the modeled population; and III) higher efficacy of risk counselling interventions within the Swiss-HCVree-trial.

Table 1 describes the model parameters associated with all scenarios including sensitivity analyses.
RESULTS

At the beginning of the screening period 4,257 MSM were enrolled in the SHCS. Simulated HCV prevalence and incidence at the beginning of the trial were 5.8% and 2.6 per 100 person-years respectively. Further characteristics of the modelled population are described in detail in (7, 10).

Projections on the effect of the pangenotypic intervention

End-of-intervention projections (Figure 2). Without intensive intervention, assuming stable risk behaviour and under the current reimbursement restrictions (F2 scenario), simulated HCV prevalence increased from 5.6% (in June 2016) to 7.7% in mid-2017. But by the end of the pangenotypic intervention (May 2017), simulated prevalence had declined to ≤2.0% across all scenarios of treatment rate in clinical-routine and high-risk behaviour in the overall population. Of note, if time from HCV infection to treatment in the overall population was ≤2 years, by May 2017, the model also predicted a decline in prevalence even without intensive intervention. Little differences between the two scenarios of high-risk behaviour in the overall population were observed in these short-term simulations.

Long-term projections (2025)(Figure 3A). If we assumed stable high-risk behaviour in the overall population, expected prevalence in 2025 without intensive interventions ranged from 13.1% to 0.7% across scenarios of treatment rate in clinical-routine. The long-term effect of the pangenotypic intervention was smaller than that at the end of the intervention. This occurred because after the intervention period, HCV-prevalence increased again. The speed of this increase was determined by treatment rate in clinical-routine and high-risk behaviour in the overall population. These variables also influenced the absolute reduction in long-term prevalence following the pangenotypic intervention, which ranged between 0.1 and 2.0 percent points. If high-risk behavior in the overall population remained stable and treatment in
clinical-routine was deferred according to the current reimbursement restriction (F2 scenario), simulated HCV-prevalence in 2025 exceeded that in 2016 by at least 5 percent points with or without intensive interventions. But if time from HCV infection to treatment in clinical-routine was ≤2 years, simulated prevalence in 2025 was lower than that in 2016. If time from HCV infection to treatment in clinical-routine was 2 years, the pangenotypic intervention reduced expected prevalence by 41% (from 4.8% without pangenotypic intervention to 2.8%) and 42% (from 1.6% to 0.9%) when assuming stable and reduced high-risk behaviour in the overall population respectively.

When time from HCV infection to treatment in clinical-routine was one year, HCV-prevalence dropped to ≤0.7%.

Cumulative number of treatment episodes (2016-2025)(Figure 3B). In the F2 scenario, the pangenotypic intervention increased the cumulative number of treatment episodes by 35% (from 214 to 288) when assuming stable high-risk behaviour in the overall population (Figure 3B). But with much shorter time from HCV infection to treatment in clinical-routine, the pangenotypic intervention was predicted to reduce treatment episodes with respect to no intensive intervention. For instance, if time from HCV infection to treatment in clinical-routine was 2 years and high-risk behaviour in the overall population stable, the pangenotypic intervention reduced the cumulative number of treatment episodes by 36% (from 678 to 431).

Projections on the effect of the Swiss-HCVree-trial

Model projections with the pangenotypic intervention and those with the Swiss-HCVree-trial were close (Supplementary Figures S1 and S2). However, as expected, the Swiss-HCVree-
trial was less effective at reducing HCV-prevalence and treatment episodes than the pangenotypic intervention. These results are reported in detail in the Supplementary Material.

In all scenarios, reduced high-risk behaviour in the overall population was more successful than either the pangenotypic intervention or the Swiss-HCVree-trial at reducing HCV-prevalence in the long-term (Figure 3 and Supplementary Figure S2A).

*Expected trajectories of HCV-prevalence, -incidence and genotype distribution with the Swiss-HCVree-trial*

Figure 4 and Supplementary Figure S3 display simulated HCV-prevalence, genotype distribution and incidence over the projection period without intensive intervention and with the Swiss-HCVree-trial. Here we set time from HCV infection to treatment in clinical-routine to reflect the F2 scenario and to 2 years. These figures illustrate the trajectories towards the time points reported in Figures 2, 3A and Supplementary Figures S1 and S2A.

If we combined stable high-risk behaviour in the overall population with the F2 scenario (Figure 4A and Supplementary Figure S3A), prevalence and incidence dropped to $<3.6\%$ and $<1.3/100$ person-years (from an incidence of 2.4 person-years in 2016) respectively over the intervention period. But prevalence and incidence rose again when the intervention ended. However, if mean time from HCV infection to treatment in clinical-routine was 2 years, prevalence and incidence dropped and remained low even after the completion of the trial (Figure 4A and Supplementary Figure S3A).

Reduced high-risk behaviour in the overall population led to similar outcomes (Figure 4B and Supplementary Figure S3B). But as expected, the post-intervention speeds of increase in prevalence and incidence were much lower in this case.
In the F2 scenario, simulated incidence with the *Swiss-HCVree-trial* surpassed that without *intensive intervention* in *mid-2019* and remained slightly above until the end of the projection period (Supplementary Figure S3).

Because only patients infected with genotypes 1 or 4 are enrolled in the *Swiss-HCVree-trial*, a comparative advantage for the spread of genotypes 2 and 3 is imminent. Figures 4C and 4D show the projected **genotype distribution** when assuming stable and reduced high-risk behaviour in the overall population.

In the F2 scenario, the proportion of infections with genotypes 2 or 3 increased from 11% in 2016 to up to 27% in 2025. Earlier HCV treatment in clinical-routine led to smaller changes in genotype distribution (Figures 4C and 4D). This occurs because treatment in clinical-routine is homogenous across genotypes. Early treatment therefore shirks the discrepancy between genotypes imposed by the *Swiss HCV trial*.

Projections with the *Swiss-HCVree-trial* restricted to SHCS participants: Supplementary Figures S4 to S7 show model projections for MSM enrolled in SHCS. As expected, these results were very close to those obtained in the main analyses (Figures 2 to 4 and Supplementary Figures S1 to S3).

*Supplementary Table S2 summarizes key simulations’ outcomes.*

**Sensitivity analyses**

The outcomes of the sensitivity analyses are reported in the supplementary material. The projected effects of the *Swiss-HCVree-trial* remained qualitatively unchanged (Supplementary Figures S4 to S7).
DISCUSSION

Principal findings

Our results suggest that intensive interventions can reduce HCV prevalence among HIV-positive MSM. Simulated prevalence dropped below 2.0% (from 5.5% in 2016) over the intervention period with the pangenotypic intervention and below 3.6% with the Swiss-HCVree-trial. But prevalence would only remain low after intensive interventions if reimbursement limitations (METAVIR≥F2) are retracted so that treatment outside intensive interventions can start much earlier after HCV diagnosis. Reductions in prevalence by year 2025 due to intensive interventions ranged between 10% and 41%. Intensive interventions also reduced the projected number of treatment episodes when time from HCV infection to treatment was ≤2 years. If we assumed stable high-risk behaviour in the overall population, the percentage of averted treatment episodes reached 36% and 24% with the pangenotypic intervention and with the Swiss-HCVree-trial respectively.

If time from HCV infection to treatment in the clinical-routine was reduced to ≤2 years, prevalence would decrease steadily even without intensive interventions. When time from HCV infection to treatment in clinical-routine was 1 year, the estimated effect of intensive interventions was negligible. This occurs because treatment rate in clinical-routine and within the intensive intervention are very similar in this case. This high treatment rates result in basic reproduction numbers smaller than 1 independently of intensive interventions. Prevalence and incidence in this situation are therefore low (<0.7% and < 0.4/100py respectively in 2025).

High costs of DAA remain a major barrier to treatment. A recent study estimated prices of DAA therapy adjusted for purchasing power parity raging between 1,861 USD and 154,227 USD (17). Independently of intensive interventions, reducing time from HCV infection to treatment in the clinical-routine to 1 year would at most double the cumulative number of
treatment episodes between 2016 and 2025 while decreasing prevalence by at least a factor of 18 over the same period. In particular, reducing time from HCV infection to treatment in clinical-routine from the scenario F2 to 1 year, combined with an intensive intervention would only increase the number of treatments by 20% by 2025. Therefore, more aggressive treatment and the relief of reimbursement restrictions could substantially reduce HCV transmission at relatively low additional costs in the long-term. The model also suggests that if treatment reimbursement restrictions remain (METAVIR \( \geq F2 \)), the Swiss-HCVree-trial would increase by at least 33% the cumulative number of treatments between 2016 and 2025 in Switzerland.

A sensitivity analysis where we increased the effectiveness of risk counselling within the Swiss-HCVree-trial resulted in a modest reduction in long-term prevalence (\( \leq 0.54 \) percent points by 2025). By contrast, sustained reductions in high-risk behaviour in the overall population, could rapidly curb the epidemic even without increasing access to treatment. This underscores the importance of sustained efforts to prevent exposure to HCV transmission. But long-lasting reductions in high-risk behaviour are hard to achieve in HIV-positive MSM on antiretroviral therapy (12). This implies the need for treatment as prevention to accompany behavioural interventions. For instance, if stabilization of high risk-behaviour is achieved, earlier treatment initiation could substantially reduce HCV prevalence.

**Strengths and limitations**

To our knowledge this is the first published study to use a mathematical model to project the population level impact of a clinical trial or other intensive interventions to tackle HCV transmission. The strengths and limitations of the core model have been discussed elsewhere (7). We believe the main strength of the mathematical model developed in the present study is that it emulates the dynamics of sexually transmitted HCV and its response to real-life interventions and to hypothetical scenarios of treatment and high-risk behaviour.
simultaneously. Moreover, our results could be generalized to other settings as regulatory drug restrictions remain in several countries (18-20) and we provide estimates independent of the particular design of the Swiss-HCVree-trial by modelling the pangenotypic intervention.

The lack of data on the role of HCV infections acquired through high-risk practices abroad could limit the accuracy of our predictions. While a phylogenetic study provided evidence for dominant domestic transmission in Switzerland (21), more detailed analyses to quantify the relative contributions of domestic and imported transmissions are needed to reach a conclusion on this matter. Nevertheless, a sensitivity analysis suggested that our results are robust to high fractions of infections due to contacts outside the modelled population. Of note, the Swiss-HCVree-trial collects data on the presumed place of HCV acquisition and we aim at performing phylogenetic studies to address this open question.

The model assumed that HCV treatment with DAAs lasted for 12 weeks for all patients. In reality grazoprevir/elbasvir treatment is recommended to last for 16 weeks in patients with pre-existing NS5A resistance associated substitutions and in some treatment experienced patients (22). However, less than 10% of all study participants are expected to fulfil these criteria.

Our model neglects factors other than differential treatment rates across genotypes that could influence genotypes distribution (e.g., changes in demographics due to migrations). Therefore we implicitly assumed the genotype distribution to be static in scenarios without the Swiss-HCVree-trial.

Finally, because model parameterization only considered data collected before the recruitment period of the Swiss-HCVree-trial, recent changes in population characteristics may have been neglected.
Outlook

We aim to assess the accuracy of our model projections by comparing them with the real end-of-study effects of the Swiss-HCVree-trial. The core transmission model is largely based on data from the SHCS and was shown to reproduce the epidemic accurately(7). However, comparing model outcomes with real data will help evaluate and improve the extent to which the model structure and underlying assumptions capture the key aspects of the dynamics of sexually transmitted HCV and its response to specific interventions.

Implications of findings

Our model projections suggest that a 1-year intensive intervention could save HCV treatment costs while boosting the benefits of long-term efforts to prevent high-risk behaviour and to increase treatment rate in clinical-routine. However, if treatment reimbursement restrictions are not relieved and the level of high-risk behaviour in the overall HIV-positive MSM population does not decrease, HCV-prevalence may double by 2025 despite intensive interventions.

The results of this study triggered the prolongation of the Swiss HCVree trial. Treatment for patients with reinfection with HCV genotypes 1 and 4 will be provided between March 2017 and January 2018.
Acknowledgments

Authors’ contributions: LSV, RDK and AR designed the study. LSV and RDK formulated the mathematical model. LSV implemented the model and performed the model analyses. JF, DB, EB, JD, MS, PS, MR, HFG contributed cohort data. LSV, RDK, JF, DB, JE, HFG, OK and AR drafted the first version of the manuscript which was then revised by all the other authors. All authors contributed to the interpretation of the results.

Statement of interests

Roger D. Kouyos received travel grants from Gilead Sciences; Jan Fehr reports support to his institution for consultancy from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck and ViiV, travel grants from Gilead, Janssen, Merck and Pfizer, and personal fees for advisory boards from the Federal Commission for Sexual Health; Andri Rauch reports support to his institution for advisory boards and/or travel grants from Janssen-Cilag, MSD, Gilead Sciences, Abbvie, and Bristol-Myers Squibb, and an unrestricted research grant from Gilead Sciences. All remuneration went to his home institution and not to Andri Rauch personally. Enos Bernasconi reports support to his institution for advisory boards from Gilead Sciences, MSD, BMS, Abbvie, ViiV Healthcare, Janssen, consultancy from Gilead and travel grants from Gilead Sciences, MSD and Abbvie. Marcel Stöckle reports support to his institution for consultancy from Roche and personal fees for board membership from AbbVie, Gilead Sciences, Janssen-Cilag, MSD and ViiV, and travel grants from Gilead Sciences, Janssen-Cilag and MSD. Patrick Schmid reports support to his institution for advisory boards from Glilead, Abbvie and BMS. Mathieu Rougemont received travel grants from BMS and Gilead. Gilles Wandeler received travel grants from Gilead and MSD. Huldrych F Günthard reports personal fees for consultancy from Gilead Sciences and Merck.
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% of patients with high-risk behaviour at enrolment who permanently stop this behaviour; **

Estimated within the model by using the rate of transition to unsafe sex and the proportion of patients with high-risk behaviour at time of HIV infection reported in (7); ***% of all HCV infections that occurred between 2000 and 2013 among MSM enrolled in HIV-care

Supplementary text figures and tables can be found in the Web Appendix
Figure legends

Figure 1. Scheme of the introduction of an intensive intervention.

Simplified representation of the distribution of HIV-positive MSM when a intensive intervention is introduced. The size of the modules do not reflect the actual relative sizes of the subpopulations.

Figure 2. End-of-intervention HCV prevalence projections.

Without intensive-intervention (red and orange bars) and with the pangenotypic intervention (blue bars) assuming stable and reduced high-risk behaviour in the overall HIV-positive MSM population.

The dashed rectangle highlights a common reimbursement restriction.

Figure 3. A)Long-term HCV prevalence, B)Cumulative treatment episodes and C)Percentage of treatment episodes averted between 2016 and 2025 by introducing the pangenotypic intervention.

Without intensive-intervention (red and orange bars) and with the pangenotypic intervention (blue bars) assuming stable and reduced high-risk behaviour in the overall HIV-positive MSM population. Overall risk behaviour refers to high-risk behaviour among HIV-positive MSM.

The dashed rectangle highlights a common reimbursement restriction.
Figure 4. Projected trajectories of HCV A&B) prevalence and C&D) genotypes distribution between 2016 and 2025 with and without the Swiss-HCVree-trial.

Assuming stable (left panels) and reduced (right panels) high-risk behaviour in the overall HIV-positive MSM population. Projections assumed standard-of-care mean time from HCV infection to treatment of 16.9 (F2 scenario) and 2 years.