The elimination of disease and burden of disease

Stephanie Popping
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The elimination of disease
and burden of disease

De eliminatie van ziekte en ziektelast

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Copromotor
Dr. D.A.M.C van de Vijver
There are so many different worlds
   So many different suns
   And we have just one world
   But we live in different ones.

*Brothers in Arms - Dire Straits*
Voor Charles
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*Party based on*  
*And*  
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GENERAL INTRODUCTION
AND OUTLINE OF THIS THESIS
Partly based on

Report from the International Viral Hepatitis Elimination Meeting (IVHEM), 17-18 November 2017, Amsterdam, The Netherlands: gaps and challenges in the WHO 2030 hepatitis C elimination framework

Journal of Virus Eradication 2018; 4:193-195

Stephanie Popping, Manal El-Sayed, Jordan Feld, Angelos Hatzakis, Margaret Hellard, Olufunmilayo Lesi, Michael Ninburg, John Ward, Charles Boucher

And

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Journal of Virus Eradication 2018; 4:193-195

Stephanie Popping, Debora Bade, Charles Boucher, Mark van der Valk, Manal El-Sayed, Olafsson Sigurour, Vana Sypsa, Timothy Morgan, Amiran Gamkrelidze, Constance Mukabatsinda, Sylvie Deuffic-Burban, Michael Ninburg, Jordan Feld, Margaret Hellard, John Ward
Hepatitis C

Hepatitis C virus (HCV) is a major cause of chronic liver disease with a significant global impact. While a recently acquired HCV infection is often asymptomatic, a persistent HCV infection is related to cirrhosis, hepatocellular carcinoma (HCC) and eventually liver failure, and death.\(^1\)\(^2\) HCV is estimated to infect 71 million people, which is ~1% of the total global population.\(^3\)\(^4\) In contrast to most other communicable diseases, the absolute burden of disease has increased in the past couple of years.\(^5\)

Progress towards HCV elimination

Since 2015, direct-acting antiviral agents (DAAs) are available. DAAs are well-tolerated and have limited side effects in contrast to the previously used pegylated interferons.\(^6\) More importantly DAAs are highly effective in curing HCV infections and thus associated with reduced morbidity.\(^7\)\(^8\) The introduction of DAAs have provided, a potential to reverse the rising burden of HCV. Consequently, the start of the DAAs resulted in a call to action highlighting the urgency for HCV elimination.

In order to eliminate HCV as a major public health threat, the World Health Organization (WHO) declared the goal of reducing new HCV infections by 90% and HCV-related liver mortality with 65% by 2030\(^4\). Although countries were encouraged to establish national and international elimination plans, by 2017, only 48% of countries reported to have elimination plans in place.\(^9\) Additionally, various gaps and challenges have arisen on the path towards achieving HCV elimination, which will briefly be outlined.

In various countries and regions, the lack of reliable epidemiological data poses a major knowledge gap in the response to the epidemic. Accurate global and regional estimates are imperative. They allow the baseline from which progress monitoring and the impact of disease reducing interventions can be made. Regional HCV prevalence varies greatly, with the highest in Egypt (>10% prevalence) and the lowest in North America and Europe.\(^10\) Moreover, different segments within population groups are affected with HCV differentially and often require focused approaches. For instance, the Canadian HCV epidemic is concentrated around birth cohorts with most people unaware of their infection, so birth-cohort screening is recommended.\(^11\)\(^12\) In contrast, in Egypt where HCV exists throughout the whole population, screening programs should be implemented more widely.\(^13\) Finally, in Australia former and current people-who-inject-drugs (PWIDs) are aware of their HCV infection, yet unaware of curative DAAs and require linkage to adequate care.\(^14\)\(^15\)
In 2015, an estimated 20% of HCV infected people (14 million) were aware of their infection. Identifying those unaware of their HCV infection is a major challenge in moving forwards towards elimination. Increasing HCV awareness is, therefore, vital and challenging as most individuals are asymptomatic or do not classify themselves as a risk group. Yet, there is limited experience on the engagement of large groups of undiagnosed individuals, an approach that is likely to vary between the different population groups. Egypt battled with millions of undiagnosed HCV-infected people and established massive screening programs. Remarkably, Egypt was the first country to include children and adolescents in these programs, serving as an example to other countries driven by the estimation of 11 million children (under the age of 15) that are infected with HCV worldwide. As Egypt is a resource limited setting, it was important to create a sustainable HCV elimination plan. The combination of presidential support and successful negotiations with several companies reduced the prices for HCV-diagnostics. Additionally, the HCV diagnostic algorithm was simplified, and point-of-care-tests were made available. The latter allowed decentralization via mobile testing units and local testing sites.

While the price of the DAAs was an issue in many countries, some countries managed to have generic DAAs available or lowered list prices. In many of those countries with a reduction in price of treatment, the bottleneck became HCV testing programmes lacking coverage due to the high price of diagnostics. This led to the absurd situation that in some countries the cost of HCV diagnostics was higher than DAA treatment.

Another barrier towards the WHO elimination goals was linkage-to-care. Several minorities face linkage-to-care issues related to stigmatization or low political commitment. As a result, service penetration and the engagement with healthcare providers is limited. In the UK, for example, where homeless persons are 50-times more likely chronically HCV infected, only 3% of those received treatment. PWIDs or ex-PWIDs are often highly stigmatized, leading to difficulties in finding healthcare services that are prepared to effectively engage with them. Finally, due to the application of non-evidence based rules, adequate treatment is not provided.

There is clear evidence that harm-reduction programs, such as needle and syringe exchange programs and opioid substitution therapy, are effective in reducing HIV and HCV incidence and are highly cost effective. Nevertheless, many countries have limited harm-reduction programs due to ongoing concerns (despite evidence to the contrary) that such initiatives may boost drug use. These concerns are particularly relevant when considering the incarcerated population. Only a few countries implement adequate preventative measures or provide HCV treatment for detainees. Currently, 90 countries have needle and syringe exchange programs in place outside prison settings.
as compared to only eight countries that do so in at least one prison setting. Healthcare providers and non-governmental organizations need to collaborate to overcome these barriers and establish harm reduction and monitoring programs to attain the WHO elimination goals.

The high cost of the viral hepatitis epidemic will continue to grow in future years if current trends in testing and treatment continue. Reaching the 2030 elimination targets by increasing testing and treatment can, however, stop these increasing costs. In fact, achieving viral hepatitis elimination will produce a positive return on investment by 2028 from savings due to the removal of indirect cost associated with viral hepatitis.

HIV

Natural course of the disease and epidemiology
The human immunodeficiency virus-1, widely known as HIV, results in a depletion of CD4+ T-lymphocytes and, over time, in an acquired immune-deficiency syndrome (AIDS) and eventually death. There is a direct link with the CD4+ T-lymphocyte count and HIV-related morbidity associated with the presence of opportunistic infections when <200 cells/µL.

Globally, an estimated 38 million people are living with HIV and this number increases annually by ~2 million new HIV infections. Similar as to HCV, regional difference occur in HIV prevalence based on the affected community and implemented prevention strategies. HIV partly shifted from a sexual transmitted infection among MSM in the early ‘80s towards a pandemic among heterosexuals or babies via mother-to-child transmission in sub-Saharan Africa. Currently, 70% of all people living with HIV (PLWH) live in sub-Saharan Africa.

HIV-care and prevention
An estimated 26 million PLWH are utilizing lifelong antiretroviral therapy (ART) as HIV cannot be cured. The earlier ART is initiated after the initial HIV infection, the lower the damage inflicted to the immune system. Early ART initiation also has public health benefits as PLWH whom are virologically suppressed cannot transmit HIV. This strategy is called treatment-as-prevention, is cost-effective and therefore a highly adopted strategy in HIV prevention.

Owing to the successes of good ARTs PLWH may have a comparable life-expectancy as to the general population. HIV can therefore be considered a chronic infection which requires a more comprehensive approach. Comprehensive HIV-care should exist of several cornerstones. First, viral replication should be supressed. Second, absence of, or minimal
drug toxicity and adverse events should take place. Third, a clinician should aim to limit
drug-drug interactions, and if so of minimal severity. Lastly, HIV-care should be convenient
and aim for a minimal to no reduction of quality of life.

**Impact of an HIV infection**

Although not surprisingly, the impact of an HIV diagnosis can be overwhelming. PLWH
may experience stigma and negative reactions on their HIV-diagnosis, resulting in
social isolation and depressive feelings. Moreover, the commitment to lifelong ART
can influence daily life as it is a constant reminder to the HIV diagnosis. PLWH may
fear the progression of the disease resulting in the development of AIDS, ART related
toxicities or experience side-effects. Even when HIV is fully suppressed there is an
association with early ageing, frailty, and HIV-related neurocognitive impairment, all
which require specialized and additional care. Subsequently, this results in a higher
burden of disease and increasing HIV-care costs.

**The state of play in the Netherlands**

**HCV**

The HCV epidemic in the Netherlands is mainly concentrated among HIV-infected MSM.
From 2000 until 2015, the HCV incidence has been stable at a rate of 1.2 per 100 person-
years, and a reinfection rate of 15 per 100 PY (range 8 to 26.5 per 100 PY). A similar trend
is observed in other Western-European countries over the last decade. MSM are at high
risk of acquiring HCV due to high risk-sexual behavior, including an excessive number of
partners combined with drug use (chemsex). In the Netherlands, contrary to many other
countries, no new HCV infections are reported among PWID.

HCV monitoring is embedded in HIV-care through annual HCV-antibodies and biannual
ALT monitoring. The HCV-PCR test is recommended when a recently acquired infection
is suspected or to confirm the presence of an HCV-infection. Recently acquired HCV
infections are treatable as the Netherlands was the first country in which the DAAs became
unrestrictedly available in 2015. Nevertheless, physicians are hesitant and await viral
clearance formed by a non-evidence-based feeling of being a suitable strategy. Although
the HCV incidence halved after the unrestricted availability of the DAAs, elimination has
not yet been obtained.

**HIV**

At the end of 2018, a total of 20,104 PLWH in the Netherlands were in care in one of
the designated HIV-treatment centers. The epidemic in the Netherlands is concentrated
among MSM. Nearly 94% of HIV-infected patients report MSM as the mode of transmission,
making it very similar to the HIV epidemic in other high-income countries.
Since 2008 there is an annual decline in the number of new HIV infections. Although MSM are often aware of their risk to acquire HIV and regularly test in places such as the sexual health clinics (GGD or One-day clinic), they still account for 60% of new annual HIV infections. Although, the majority of patients was in care in an early stage of the disease, there remains a portion of patients presenting late in the infection, i.e., with CD4-cells<350µL or even AIDS. PLWH presenting late in care are often elderly, non-Western migrants, and heterosexuals. This population is often unaware of the previously acquired risk for HIV, are asymptomatic, or ashamed of a possible diagnosis.

Aim and outline of this thesis

**Elimination of HCV and the burden of disease for HIV**

This thesis discusses two viral diseases, HCV a curable disease and HIV a chronic infection. Both HCV and HIV have a tremendous public health impact, affecting millions of people worldwide. The treatment for HCV is expensive and for HIV lifelong, with additional care often requiring enormous health care utilization and subsequently cost. Elimination of HCV as disease and the burden of disease for HIV would, therefore, not only increase individuals’ health benefits but also reduce health care costs to the entire population.

Both the WHO and UNAIDS established elimination goals to affect the public health threat of both infections. The WHO recommends the reduction of 90% of new HCV infections and 65% of liver-related mortality by 2030. The UNAIDS recommends 90% of all PLWH aware of their diagnosis, from those 90% on ART, and from PLWH on ART 90% should have viral suppression by 2020. These goals, recently, further increased to 95% by 2030. The pledge from both organizations to eliminate these viral diseases provided the momentum for the elimination movement. Many stakeholders gathered to establish national and international elimination plans. Despite great efforts to inform the public, many people are unaware of their infection or did not access treatment, which subsequently leads to increases in health care costs. This thesis, therefore, aims to contribute to the elimination of disease and burden of disease taking those costs into consideration. The first two parts of this thesis focusses on the elimination of and barriers to HCV elimination. Part 1 outlines several elimination strategies which reduce new infections and cost. Moreover, Part 1 aims to provide insight into the HCV transmission dynamics in the Netherlands optimizing elimination strategies. More specifically, in Chapter 2 the effect of immediate DAA therapy compared to delaying therapy on the HCV incidence, sequalae, and overall costs among HIV co-infected MSM in the Netherlands is investigated. As HCV reinfections in the HIV-infected MSM population are soaring Chapter 3 outlines the cost-effectiveness of targeted monitoring strategies among previously HCV infected
HIV co-infected MSM. Although the HCV incidence halved over time, elimination was not yet obtained in the Netherlands. Therefore, Chapter 4 aims to gain more insight into the transmission dynamics of recently acquired HCV infections in the MSM population. Moreover, the effect of the unrestricted DAA use on HCV transmission is studied.

Part 2 aims to investigate if resistance to DAAs proposes a barrier towards HCV elimination. Chapter 5 outlines why DAA resistance can jeopardize HCV elimination efforts and that resistance surveillance is essential to measure the effect and occurrence of resistance. Chapter 6 shows the rapid spread of a resistant variant among one third of MSM with a recently acquired HCV infection.

In Part 3 of this thesis the elimination of the burden of disease for HIV will be highlighted. Although the Netherlands are on track for the UNAIDS 90/90/90 goals still half of PLWH present late in care. Late presentation is not only associated with an increased morbidity and mortality, but it also jeopardizes elimination efforts as HIV transmission may continuously occur. Importantly, late presentation is a global issue, which needs addressing. Chapter 7 of this thesis highlights the additional short- and long term direct medical costs associated with late and very late presenting in HIV-care. Moreover, Chapter 7 identifies which patient population is associated with late presentation. As HIV is no longer a life-threatening disease, but a chronic infection, for which a more comprehensive approach for care is required. Chapter 8 concentrates on the quality of life of PLWH in two Western European countries to determine the currently experienced burden of disease for HIV.

Finally, Chapter 9 provides a general discussion of the data describes in this thesis and highlights results that could be of specific interest for future research.
Part 1
EARLY TREATMENT OF ACUTE HEPATITIS C INFECTION IS COST-EFFECTIVE IN HIV-INFECTED MEN-WHO-HAVE-SEX-WITH-MEN
Abstract

Introduction: treatment of hepatitis C virus infections (HCV) with direct acting antivirals (DAA) can prevent new infections since cured individuals cannot transmit HCV. However, as DAAs are expensive, many countries defer treatment to advances stages of fibrosis, which results in ongoing transmission. We assessed the epidemiological impact and cost-effectiveness of treatment initiation in different stages of infection in the Netherlands where the epidemic is mainly concentrated among HIV-infected MSMs.

Methods: we calibrated a deterministic mathematical model to the Dutch HCV epidemic among HIV-infected MSM to compare three different DAA treatment scenarios: 1) immediate treatment, 2) treatment delayed to chronic infection allowing spontaneous clearance to occur, 3) treatment delayed until F2 fibrosis stage. All scenarios are simulated from 2015 onwards. Total costs, quality adjusted life years (QALY), incremental cost-effectiveness ratios (ICERs), and epidemiological impact were calculated from a provider perspective over a lifetime horizon. We used a DAA price of €35,000 and 3% discounting rates for cost and QALYs.

Results: immediate DAA treatment lowers the incidence from 1.2/100 person-years to 0.2/100 person-years (interquartile range 0.1 – 0.2) and the prevalence from 5.0/100 person-years to 0.5/100 person-years (0.4 – 0.6) after 20 years. Delayed treatment awaiting spontaneous clearance will result in a similar reduction. However, further delayed treatment to F2 will increases the incidence and prevalence. Earlier treatment will cost society €68.3 and €75.1 million over a lifetime for immediate and awaiting until the chronic stage, respectively. The cost will increase if treatment is further delayed until F2 to €98.4 million. Immediate treatment will prevent 7070 new infections and gains 3419 (3019 - 3854) QALYs compared with F2 treatment resulting in a cost saving ICER. Treatment in the chronic stage is however dominated.

Conclusion: early DAA treatment for HIV-infected MSM is an excellent and sustainable tool to meet the WHO goal of eliminating HCV in 2030.
Introduction

Treatment of hepatitis C virus (HCV) infections has dramatically improved since the advent of well-tolerated direct acting antiviral agents (DAAs). DAA treatment results in a 90-95% sustained virological response (SVR), which is associated with strongly reduced morbidity and cure. Importantly, as individuals that are cured cannot transmit HCV to others, DAAs can be used as prevention strategy. Apart from modelling studies, this was shown in a recent study in the Netherlands where new HCV infections were reduced by 70% after widespread use of DAAs. The World Health Organization (WHO) shares the optimism that DAAs can prevent new infections and declared an ambitious target of ending HCV as a public health threat in 2030.

A key challenge in prevention of HCV is the timing of start of DAA treatment. As DAAs are expensive, many countries defer treatment to advances stages of fibrosis, which can result in continued transmission of the virus. In countries that reimburse expensive DAAs, patients usually start treatment several months after the presumed date of infection to allow spontaneous clearance (15-20% of patients). Importantly, high-risk individuals can continue HCV transmission during that time frame.

In this study we assessed the epidemiological impact and cost-effectiveness of start of treatment in different stages of infection. For this purpose, we used the Netherlands, where HIV-infected men-who-have-sex-with-men (MSM) account for 94% of the new HCV infections. MSM are at high-risk of acquiring HCV due to high-risk sexual behaviour, including an excessive number of partners combined with drug use. In the Netherlands, contrary to many other countries, no new HCV infections are reported among injecting drug users (IDU). A key advantage of the Netherlands is that DAAs are reimbursed for all HCV stages since 2016. However, before 2016, use of DAAs was restricted to METAVIR F2 stage. The epidemiological impact of DAAs has been reported for the scenario where DAAs were restricted to advanced stages of fibrosis (before 2016) and after DAAs were used irrespective of the stage of fibrosis (after 2016). Therefore, we could calibrate our model to the epidemiological impact of unrestricted DAA treatment after a period of restricted DAAs by assuming that the incidence of HCV would remain comparable to the epidemic before 2016 and we could calibrate the model to the scenario of unrestricted DAAs by including the epidemiological impact after 2016.
Methods

Study design and population
The HIV epidemic in the Netherlands is concentrated among MSM, with nearly 94% of infected patients reporting MSM as the mode of transmission, making it very similar to the HIV epidemic in other high-income countries.60,61 This young epidemic is characterized with incidence rates of 1/100 persons-years.69,70 In addition, HCV reinfections are a major concern in this population, with incidence rates of 7.3/100 person-years after cure.71 The epidemic is well described through a national HIV database (ATHENA cohort), which contains anonymized demographic and clinical data of >98% of patients in HIV care in the 27 treatment centres in the Netherlands.72 We developed a deterministic mathematical model to represent the HCV/HIV epidemic among MSM in the Netherlands.

Model parametrisation and calibration
We calibrated our model to the Dutch HIV epidemic including data on HCV from the Dutch Acute HCV in HIV study (DAHHS).48,49,72-74 Our calibration is based on the estimated Dutch MSM population size, the percentage of individuals co-infected with HCV, a stable HCV incidence rate of 1.2 per 100 person-years, and a reinfection rate of 15 per 100 PY (range 8 to 26.5 per 100 PY) (Table 1, S1 Fig. S1 Text).48-50,75,76 We accounted for the population effect of widespread DAA use by validating our model’s projected incidence in 2016 with published Dutch HCV incidence data of 2016 (0.4-1.0/100 PY).58,77 With Monte Carlo filtering techniques a total of 132 out of 100,000 simulations remained that matched the Dutch HCV epidemic among HIV-infected MSM (S1 Table).78-80

Our model stratifies disease progression into individuals that spontaneously clear the virus (15-20% of cases), three stages of progressive fibrosis (METAVIR stages F0-F3), and two stages of cirrhosis (stage F4 sub-divided in compensated- and decompensated cirrhosis).66 From stage F3, F4 compensated and F4 decompensated cirrhosis patients can develop a hepatocellular carcinoma (HCC) with a rate of 2-5%.

The rate by which HCV/HIV co-infected individuals progress from a particular stage of fibrosis to a more advanced stage of fibrosis is approximately 10% per year (this rate of progression results in a probability of having cirrhosis –stage F4- of 20.8% to 48.5% after 20 to 30 years, respectively)(S2 Table).81 Due to a shortage of donors, liver transplantation has not been performed in HIV/HCV co-infected individuals in the Netherlands and is, therefore not considered in the model. We assumed that during HCV treatment individuals are virological suppressed and do not transmit HCV to others. In our model before 2012, chronically infected patients in F2 through F4 fibrosis stages were treated with pegylated interferon and ribavirin. Between 2012 and 2015, boceprevir or telaprevir
in addition to pegylated interferon and ribavirin, was prescribed to chronically infected patients. We assumed that until 2015, between 67% and 75% of patients were treated for 24 weeks with pegylated interferon and ribavirin (other patients declined treatment) as in agreement with the treatment guidelines that were in place. After 2015, pegylated interferon was no longer considered, since DAAs were reimbursed for all stages of HCV infection in the Netherlands.

In our model there are four different risk groups in which individuals have a different number of HIV-infected partners per years (S2 Table).79

**Different treatment scenarios**

All HIV-infected MSM undergo HCV screening, using a biannual ALT and annual antibody test, in which the model assumes that approximate 85% of the HCV infections are diagnosed.83,84,99 After diagnosis, treatment is given according to three treatment scenarios evaluated in the model from 2015 onwards. In the first scenario DAAs are given immediately after diagnosis in the acute stage of HCV (immediate treatment). The model accounts a median time of 18.1 weeks (range 16.5 – 25 weeks) from transmission until treatment initiation of acute HCV.74 In the second scenario, treatment is delayed until the chronic stage, awaiting spontaneous clearance varying from 40-170 days (chronic treatment).85 In the third scenario DAAs are delayed until an advanced stage of HCV infection, F2 METAVIR (delayed F2 treatment) (S2 Fig).

In our model all individuals with that do not have cirrhosis receive a 12-week DAA treatment course. SVR rates for treatment ranged between 89-100% with a median of 94% (Table 1). If a SVR is not achieved individuals are re-treated with a 12-week DAA course. During the cirrhotic stage DAA treatment is prolonged until 16 weeks with SVR rates for treatment between 80-95%.

**Cost and QALY estimates**

The cost-effectiveness analysis was performed from a provider perspective. Each compartment in our deterministic model was assigned a cost and quality adjusted life year (QALY) score (Table 1). Costs for HCV monitoring and treatment were collected among the six Academic Medical Centres in the Netherlands. Our model used a DAA price of €35,000 for a 12-week treatment course, which is varied in the sensitivity analysis. QALY weights were obtained from data of the Dutch HIV/HCV co-infected MSM cohort (DAHHS).88 HIV mono-infected MSM are assumed to have a QALY of 0.94.95 The model considers the HCV/HIV co-infection utility-score to be an interaction between the HIV- mono and HCV-mono infected utility scores. HCV/HIV co-infected MSM are assumed to have a utility score of 0.84 during F0-F3 stage. QALY scores during DAA treatment remained similar. After
resolving the HCV infection, the QALY score returned to that of an HIV mono-infected (i.e. 0.94). Both costs and QALY scores were discounted at 3% per year. For this study, we used a willingness-to-pay threshold of €20,000 per QALY.

### Table 1. Model parameters and ranges used in hepatitis C (HCV) transmission model

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<th>Model Parameters of HCV transmission model among Dutch MSM</th>
<th>Range/number (median)</th>
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<td>Annual HIV diagnoses among MSM per time-period</td>
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<td>2002-2014</td>
<td>720-740</td>
</tr>
<tr>
<td>2015</td>
<td>620</td>
</tr>
<tr>
<td>2016</td>
<td>580</td>
</tr>
<tr>
<td>Susceptible HIV-infected MSMs in 2002</td>
<td>3800</td>
</tr>
<tr>
<td>Patients with HCV in 2002</td>
<td>2-10%</td>
</tr>
<tr>
<td>Mortality rate HIV patients ≥350 CD4 count</td>
<td>1/45%</td>
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<tr>
<td>Transmissibility of HCV</td>
<td>0.01-0.05</td>
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<td>Diagnosed percentage per HCV testing moment</td>
<td>70-100%</td>
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<tr>
<td>Clearance rate</td>
<td>15-25%</td>
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<tr>
<td>Time to clearance</td>
<td>40-170 days</td>
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<tr>
<td>Reinfection rate</td>
<td>8-26.5%, per year</td>
</tr>
<tr>
<td>Time from transmission until treatment (acute HCV)</td>
<td>16.5 - 25 weeks</td>
</tr>
<tr>
<td>Time from transmission until treatment (F0 chronic)</td>
<td>20.4 - 54.2 weeks</td>
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<td>Patients in stage F3, F4 in 2002</td>
<td>10-30%</td>
</tr>
<tr>
<td>HCC rate</td>
<td>2-5%</td>
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<tr>
<td><strong>Treatment parameters</strong></td>
<td></td>
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<tr>
<td>SVR, DAA F0-F3</td>
<td>89-100%</td>
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<td>Treatment duration F0-F3</td>
<td>12 weeks</td>
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<td>SVR, DAA cirrhosis</td>
<td>80-95%</td>
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<td>Treatment duration F4 compensated and decompensated</td>
<td>16 weeks</td>
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<td>Re-treatment duration F0-F3</td>
<td>12 weeks</td>
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<td>Re-treatment duration F4 compensated and decompensated</td>
<td>16 weeks</td>
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<td><strong>Quality of Life</strong></td>
<td>Utility score</td>
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<td>HIV mono-infection</td>
<td>0.94%</td>
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<td>Acute HCV infection</td>
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<td>HCV F0-F3 stage</td>
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<td>Compensated cirrhosis</td>
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<td>Decompensated cirrhosis</td>
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<td>DAA based therapy</td>
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<th>Model Parameters of HCV transmission model among Dutch MSM</th>
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<td>Costs</td>
<td>Price in €</td>
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<td>Doctors visit</td>
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</tr>
<tr>
<td>HCV RNA</td>
<td>105 - 225 ¥</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>130 - 252 ¥</td>
</tr>
<tr>
<td>Ultrasound of the liver</td>
<td>90 - 226 ¥</td>
</tr>
<tr>
<td>Biochemistry and liver function tests</td>
<td>38 – 46 ¥</td>
</tr>
<tr>
<td>F3 additional costs per year **</td>
<td>808 ¥</td>
</tr>
<tr>
<td>F4 additional costs per year **</td>
<td>808 ¥</td>
</tr>
<tr>
<td>DAA regimen 12 weeks</td>
<td>35,000 ¥</td>
</tr>
</tbody>
</table>


* Successfully treated patients who achieved viral suppression and attained a CD4+ cell count of at least 350 cells/µl within 1 year of starting ART had a normal life expectancy, with a 35-year-old HIV-infected person estimated to live to about 80 years on average

** Additional costs per year are based on the abdominal echo’s (HCC screening), additional doctor appointments and biochemistry

¥ Weeks are based on the time that a patient needs to be diagnosed (16.5-25 weeks*) with an additional number of weeks that is “waited” until a patient reach possible spontaneous clearance. In the model we “wait” an additional 3-3.5 months for spontaneously clearance (+/- 90 days)

§ The model considers the HCV/HIV co-infection utility score to be an interaction between the utility for HIV mono and HCV mono scores. The utility scores are varied in the sensitivity analysis

† Dutch data summarized out of different academic hospitals in the Netherlands

HIV-infected MSM are co-infected with HCV at a median age of 40 years. In addition, an HIV-infected MSM with CD4 >350 cells/µl has a life expectancy of 80 years. Therefore, we used a 40-year time horizon to calculate the epidemiological impact and economic outcomes. The reported numbers are the median values with the corresponding interquartile range between brackets. Prices are notated in euros (€).

Sensitivity analysis and uncertainties

We performed a one-way sensitivity analysis of the incremental cost-effectiveness ratios comparing the immediate treatment scenario with the delayed F2 treatment scenario. Several key input variables were varied: cost of DAAs (€5,000 - €50,000), spontaneous clearance rate (5-10% - 15-30%), discounting rates (0 – 5%), HCV testing intervals (3 – 12 months), QALY score during DAA treatment (0.84 – 0.94), an increase in the number of high-risk MSM that are at risk of acquiring HCV (up to 6500 individuals) since the introduction of HIV pre-exposure prophylaxis (PrEP) and the impact of continuing transmission from undiagnosed HCV-infected individuals (up to 100 individuals that remain undiagnosed). HIV PrEP
users should be taken into account since HCV prevalence among HIV-negative PrEP users is increasing, in contrast to a stabilizing prevalence among HIV-negative MSM. As data that we could use for calibration of HCV among HIV-uninfected MSM and PrEP users is not fully available we established a sensitivity analysis.

Results

Model projections
Epidemiological impact of different treatment scenarios
Before 2015 there was a stabilizing incidence of 1.2/100 person-years and prevalence of 5.0%. After starting our treatment scenarios, the model projected an increasing, but further stabilizing incidence at 1.4/100 person-years (IQR 1.2 – 1.7) for the delayed F2 treatment scenario after 20 years. The prevalence is projected to increase over time to 9.5% (8.8 – 10.5) in 2025 and to 11.7% (10.3 – 13.3) in 2035 (Fig. 1).

Treatment in the chronic stage of infection, after awaiting clearance, will reduce the incidence by 68% to 0.5/100 person-years (0.4 – 0.5) in 2025 and by 84% in 2035 to 0.2 /100 person-years (0.2 – 0.3) compared with delayed F2 treatment. The prevalence will reduce over time by 87% to 1.2% (1.1 – 1.4) in 2025 and by 95% to 0.5% (0.4 – 0.7) in 2035. Over the 40-year time horizon, a total of 7070 new infections were prevented in the chronic treatment scenario as to compared with the delayed F2 treatment scenario.

Immediate treatment will further reduce the incidence by 73% to 0.4/100 person-years (0.3 – 0.4) in 2025 and by 88% to 0.2/100 person-years (0.1 – 0.2) in 2035 and the prevalence by 89% to 1.0% (0.9 – 1.1) in 2025 and by 96% to 0.4% (0.3 – 0.5) in 2035. A total number of 7457 new infections were prevented by immediate treatment compared with delayed F2 treatment over 40 years.

Impact of different treatment scenarios on Hepatocellular carcinoma
Our model projected an increasing HCC incidence rate for delayed F2 treatment up to 2032 before it slowly stabilizes and starts to decrease. This increase is also attributed to the removal of pegylated interferon as treatment for acute HCV infections. More individuals will therefore enter an F3 stage and are at risk for HCC. Delayed F2 treatment will result in an HCC incidence of 0.42 per 1000 person-years (IQR 0.28 – 0.59). Immediate treatment and chronic treatment will dramatically reduce the incidence rates to 0.01 per 1000 person-years (0.00 – 0.02) and 0.01 per 1000 person-years (0.01 - 0.03) after 40 years, respectively (S3 Fig).
Fig 1. Short-term epidemiological hepatitis C virus impact among HIV-infected MSM

In the upper figure, the median hepatitis C virus incidence is projected and in the lower figure the median hepatitis C virus prevalence. Three different treatment scenarios were simulated over a short-term period of 20 years. F2 - delaying treatment until a F2 fibrosis stage, F0 chronic- awaiting the period of spontaneously clearance, and Acute HCV - treatment in the acute stage of an HCV infection.
<table>
<thead>
<tr>
<th>Scenario*</th>
<th>HCV infections averted at 40yr</th>
<th>HCV Prevalence reduction at 20yr</th>
<th>Total costs, Euro’s € (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>-</td>
<td>-</td>
<td>€ 98.4</td>
</tr>
<tr>
<td>F0 acute</td>
<td>7457</td>
<td>97%</td>
<td>€ 68.3</td>
</tr>
<tr>
<td>F0 chronic</td>
<td>7070</td>
<td>96%</td>
<td>€ 75.1</td>
</tr>
</tbody>
</table>

The reported numbers are median values with the corresponding interquartile ranges between brackets.

Three different scenarios are modelled. Scenario F2 - delaying treatment until a F2 fibrosis stage, F0 chronic- awaiting the period of spontaneously clearance, and Acute HCV - treatment in the acute stage of an HCV infection. Abbreviations: HCV: hepatitis C, QALYs: Quality Adjusted Life Years, ICER: incremental cost-effectiveness ratio.

**Cost-effectiveness**

Our model projected that the HCV epidemic among Dutch HIV co-infected MSMs would cost €98.4 million (IQR €87.9 – 112.9) with delayed F2 treatment over a lifetime (Table 2). However, immediate treatment and treatment according to the chronic scenario would cost far less, €68.3 million (62.9 – 75.1) and €75.2 million (69.3 – 84.3) over 40 years, respectively. The projected cost reduction is mainly attributed to the infections prevented by timely initiation of DAA treatment. There were 3,419 QALYs gained (3,019 – 3,854) in the immediate treatment scenario compared with delayed F2 treatment. Combined with the lower cost of immediate treatment over the 40-year time horizon, this resulted in the immediate treatment scenario being cost-saving (Table 2). The chronic treatment scenario is, however, dominated by immediate treatment, given that chronic treatment was more costly and resulted in fewer QALYs gained than immediate treatment. In addition, awaiting spontaneous clearance and therefore delaying treatment is associated with increased costs €6.9 million and a decrease of 47 (34 – 71) QALYs as compared with immediate treatment.

**Sensitivity analysis**

We conducted a one-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) of immediate treatment compared with the delayed F2 treatment scenario (Fig 2). The ICER most strongly depends on the testing intervals, and immediate treatment is more cost saving when the testing interval is three-monthly, and cost-effective at €6,348 per QALY gained for annual testing.
Table 2. Results of the main cost-effectiveness analysis of three different DAA treatment scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>HCV infections averted at 40yr</th>
<th>HCV Prevalence reduction at 20yr</th>
<th>Total costs, Euro’s € (millions)</th>
<th>QALYs x 1000</th>
<th>Incremental costs Euro’s € (millions)</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>-</td>
<td>-</td>
<td>€ 98.4</td>
<td>331.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F0 acute</td>
<td>7457</td>
<td>97%</td>
<td>€ 68.3</td>
<td>334.7</td>
<td>-€ 30.0</td>
<td>3425</td>
<td>cost saving</td>
</tr>
<tr>
<td>F0 chronic</td>
<td>7070</td>
<td>96%</td>
<td>€ 75.1</td>
<td>334.6</td>
<td>€ 6.9</td>
<td>-47</td>
<td>dominated</td>
</tr>
</tbody>
</table>

The reported numbers are median values with the corresponding interquartile ranges between brackets. Three different scenarios are modelled. Scenario F2 - delaying treatment until a F2 fibrosis stage, F0 chronic - awaiting the period of spontaneously clearance, and Acute HCV - treatment in the acute stage of an HCV infection. Abbreviations: HCV: hepatitis C, QALYs: Quality Adjusted Life Years, ICER: incremental cost-effectiveness ratio.

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Although our sensitivity analysis showed that the precise epidemiological impact of the DAAs on the HCV incidence changes, in both situations immediate start of DAA treatment as compared with delaying to F2 stage remained cost-saving. Hence it is of utmost importance that all high-risk MSM, regardless of HIV status, are regularly screened for HCV to maintain the treatment as prevention effect for DAAs. While the DAA price influences the ICER, immediate treatment remains cost-saving.

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**Fig 2. One-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) (€/QALY) of DAA treatment**

DAA treatment in the acute stage and delayed F2 stage of and HCV infection are compared with varying different key parameters. The bars show variation in the ICER stated in euros.

Discussion

We used a deterministic mathematical model to compare the economical and epidemiological impact of three different DAA treatment scenarios among HIV-infected MSM in the Netherlands. The key finding of our study is that treatment of acute HCV infections (immediate treatment scenario) is a cost-saving intervention since immediate treatment will save money and increases health benefits in the long term. Moreover, it will reduce HCV incidence among HIV-infected MSM, despite the high reinfection rates. This strongly indicates that DAAs treatment for acute HCV is a suitable and financially sustainable tool to reach viral hepatitis elimination goals as defined by the WHO (i.e., 90% reduction in new chronic infections and 65% reduction in mortality).

Our study showed that the size of the future HCV epidemic is highly influenced by treatment initiation time. A decrease of incidence and prevalence when treating individuals in earlier stages of the HCV disease is predicted. On the contrary, an increase in incidence, prevalence, and a higher number of HCC is predicted when further delaying treatment. Therefore, treatment should be administrated in a timely manner to avoid further transmission and to reduce future health care related costs. In addition, awaiting clearance before initiating treatment is less beneficial and not suitable for the HIV co-infected MSM population as compared with immediate treatment upon diagnosis.

Our findings are important for treatment and for public health as they indicate an economic advantage of DAA treatment in the early stages of infection as compared with deferring treatment. In many countries the extraordinarily high cost of DAAs resulted in restrictive reimbursement policies. Restrictions can be based on fibrosis, co-infection and substance abuse. Still, countries continue to delay DAA treatment until F2 or even F3 stages. Our model concludes that limited access and delaying treatment will only increase incidence, prevalence, and related costs.

Several cost-effectiveness studies on the impact of DAAs on HCV were performed among people who inject drugs (PWID). These studies found that DAAs are cost-effective among PWID. However, the results of these studies cannot be compared with our model as PWID are not comparable with HIV-infected MSM. HIV-infected MSM are unlike PWID, as they are often well-defined and in regular HIV care. In addition, risk behaviour and reinfection rates differ.

Our findings agree with two other modelling studies, one from the United Kingdom and the other from Switzerland, which predicted the epidemiological impact of DAAs on the HCV epidemic among HIV-infected MSM. However, our study measured not only the
epidemiological impact, but also the cost-effectiveness. The WHO recommends conducting cost-effectiveness studies, as one of the pillars in their elimination goals, to aim for long-term program sustainability. In addition, due to the new Dutch Acute HCV in HIV incidence data, we were able to measure the population-level effect of the DAAs after an unrestricted roll-out.58

A key strength of our model is that we are, to our knowledge, the first cost-effectiveness study that includes the population benefits of DAAs started in different stages of fibrosis obtained from a real-world setting.58 Another strength is that our model is based on data of the well monitored HIV epidemic in the Netherlands.60 As a consequence, our mathematical model is calibrated to complete and accurate data on the annual number of (newly) diagnosed HIV-infected MSM and data on incident HCV infections among people living with HIV in the Netherlands. Combined, these two strengths allowed us to make accurate predictions of the effect of unrestricted access to DAAs and the effect of deferred treatment, on the HCV epidemic among HIV-infected MSMs on a population level which captures also the “unknown” influence of treatment of other risk groups in the Netherlands interacting with the HIV-infected MSM population.

In our model we did not specify the different DAA regimens and different genotypes. Genotype was known to influence the response to pegylated interferon containing regimens.6 However, due to the excellent efficacy of the DAAs, regimens have high SVR rates irrespective of the genotype. In our model we used SVR rates of 89-100% which agree with reported ranges for DAA treatment of non-cirrhotic stages of infection (F0-F3). We used a 12 week regimen in our model since most treatment regimens are recommended 12 weeks regardless of genotype or fibrosis stage.92

The price of DAAs is known to vary between countries and between regimens. We therefore conducted a sensitivity analysis varying the DAA price between €5,000 and €50,000 (Fig 2). A lower DAA price results in a more cost-saving ICER. Our sensitivity analysis also showed that the cost-effectiveness of DAA treatment strongly depends on the HCV testing frequency in routine clinical care. HIV-infected MSM are bi-annually screened for HCV. More frequent testing will, however, lead to timely identification of acute HCV infections and more prevented infections.118

In the Netherlands, the epidemic is solely driven by MSM and new infections due to injecting-drug use (IDU) are almost zero.35,56 We do realize that there are countries in which IDU remains a problem and that interaction between MSM and IDU may occur. The study of Virologeux et al. assessed the influence of interaction between the IDU population and the HIV-infected MSM population and no difference was found regarding elimination outcome if there would be a limited amount of interaction.119
Conclusion

In conclusion, our study shows that DAA treatment for acute HCV-infected individuals is a cost-saving prevention approach that strongly reduces the HCV epidemic among HIV-infected MSM, despite high reinfection rates. Furthermore, shows our study that although earlier treatment (F0 chronic) is dominated by acute treatment, this is still highly favourable compared with delayed F2 treatment. Concerns about economic sustainability of expensive DAAs should, therefore, not be a reason to restrict DAAs to more advanced stages of fibrosis. Moreover, our study addresses the consequences of delaying treatment in a population with high-risk behaviour while adequate treatment is available. We concluded that DAAs are an excellent and sustainable tool to meet the WHO elimination goals and that all HIV-infected MSM should have universal accessibility regardless of infectious stage.
Supporting information

S1 Table. Variables used to calibrate and accept simulations using the Monte Carlo filtering technique

<table>
<thead>
<tr>
<th>Parameter used to accept simulations</th>
<th>Values accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HIV-HCV co-infections in 2014</td>
<td>450-850⁴⁹</td>
</tr>
<tr>
<td>Annual number of new HIV-HCV co-infections (2014)</td>
<td>100-150⁴⁸</td>
</tr>
<tr>
<td>Incidence rate in 2012 through 2014</td>
<td>11-13 per 1,000 person-years⁵⁰</td>
</tr>
<tr>
<td>Incidence rate after DAA roll-out 2016</td>
<td>4 – 10 per 1000 person-years⁷⁷,¹²⁰</td>
</tr>
<tr>
<td>Reinfection rate in 2014</td>
<td>8 – 26.5% per year⁵¹,⁷¹</td>
</tr>
</tbody>
</table>
Comparison of the projected number of MSM that are diagnosed with HIV (black bullets and line) and the actual number of MSM diagnosed as reported by the Dutch HIV monitoring foundation (Upper figure). Comparison of the incidence rate of the Dutch population over time and the median simulations of our model. At T=2014 the first DAAs were introduced in the Netherlands for F2/F3 patients and treatment in clinical trials. In 2015 DAAs became unrestricted available and in 2016 a new incidence data was available (Lower figure).
### S2 Table. Parameters in the model

<table>
<thead>
<tr>
<th>Parameters of epidemic among HIV-infected MSM</th>
<th>Range [source/rationale]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual new sexual partners</strong></td>
<td>[Calibrated]</td>
</tr>
<tr>
<td>Highest risk group</td>
<td>20-100</td>
</tr>
<tr>
<td>Risk group 2</td>
<td>5-15</td>
</tr>
<tr>
<td>Risk group 3</td>
<td>1-4</td>
</tr>
<tr>
<td>Risk group 4</td>
<td>0.1 – 0.9</td>
</tr>
<tr>
<td><strong>Proportion per risk group</strong></td>
<td>[Calibrated]</td>
</tr>
<tr>
<td>Highest risk group</td>
<td>- 0.14</td>
</tr>
<tr>
<td>Risk group 2</td>
<td>- 0.2</td>
</tr>
<tr>
<td>Risk group 3</td>
<td>0-0.3</td>
</tr>
<tr>
<td>Risk group 4</td>
<td>0.4-0.9</td>
</tr>
<tr>
<td>Rate of assortative mixing</td>
<td>0-0.8 [Calibrated]</td>
</tr>
<tr>
<td>Patients in stage F3, F4 in 2002</td>
<td>10%-30% [Calibrated]</td>
</tr>
<tr>
<td><strong>Life Expectancy and mortality</strong></td>
<td></td>
</tr>
<tr>
<td>HIV-infected men CD4&gt;350</td>
<td>80 years[^82]</td>
</tr>
<tr>
<td>HIV/HCV co-infected (F0-F3 stage)</td>
<td>80 years[^82]</td>
</tr>
<tr>
<td>HIV/HCV co-infected compensated cirrhosis</td>
<td>0.024-0.055 per year[^21]</td>
</tr>
<tr>
<td>Life expectancy HIV/HCV decompensated cirrhosis</td>
<td>0.019-0.35 per year[^22]</td>
</tr>
<tr>
<td><strong>Disease progression</strong></td>
<td></td>
</tr>
<tr>
<td>F0 to F1</td>
<td>0.098 – 0.122, per year[^61]</td>
</tr>
<tr>
<td>F1 to F2</td>
<td>0.095 – 0.140, per year[^51]</td>
</tr>
<tr>
<td>F2 to F3</td>
<td>0.097 – 0.159, per year[^61]</td>
</tr>
<tr>
<td>F3 to Compensated cirrhosis</td>
<td>0.098 – 0.135, per year[^51]</td>
</tr>
<tr>
<td>Compensated to decompensated cirrhosis</td>
<td>0.029 – 0.063, per year[^22]</td>
</tr>
<tr>
<td>Compensated to decompensated cirrhosis</td>
<td>0.029 – 0.063, per year[^22]</td>
</tr>
<tr>
<td>Cirrhosis to Hepatocellular carcinoma</td>
<td>0.01 – 0.03, per year[^22]</td>
</tr>
<tr>
<td>Transplantations</td>
<td>0 per year</td>
</tr>
<tr>
<td><strong>Additional cost to delayed treatment stage</strong></td>
<td></td>
</tr>
<tr>
<td>Cost of HCC (including hospitalization, treatment, surgery, and care until death)</td>
<td>€67,591 – €233,573 per patient[^23,24]</td>
</tr>
</tbody>
</table>
S2 Fig. Simplified diagram capturing the HCV transmission model among HIV-infected MSM evaluating different treatment scenarios

Individuals can be treated during an acute HCV infection (Scenario 1), treatment is delayed until possible spontaneous clearance (Scenario 2), or individuals are treated according to the delayed F2 treatment scenario (Scenario 3). Individuals progress through the natural course of disease over time.

Abbreviations: DAA: direct-acting antivirals, F0-F3: fibrosis score METAVIR, HCC: hepatocellular carcinoma

S3 Fig. Cumulative avoided hepatitis C related hepatocellular carcinoma compared with delayed F2 treatment

Simulated Hepatitis C related hepatocellular carcinoma that can be avoided when treatment is administrated timely instead of delayed until F2 stage among HIV-infected MSM. F0 chronic, initiating treatment in the chronic phase of infection, waiting for the infection to spontaneously clear. T=0 (year 2015) start of intervention.
S4 Fig. Influence of removal of pegylated-interferon as treatment of acute hepatitis C on the incidence among HIV-infected men-who-have-sex-with-men

In current guidelines pegylated-interferon is no longer recommended in the acute stage of hepatitis C virus (HCV) infection. However, individuals treated and cured with pegylated-interferon during the acute stage of HCV infection, could not further transmit HCV. The removal of pegylated-interferon and delaying DAA treatment until F2, therefore has a negative epidemiological impact. We conducted an uncertainty analysis, in which DAA treatment is delayed until F2 stage and pegylated-interferon is a possible option during the acute stage of HCV. In addition, the incidence reduction when treatment is provided immediately and during the F0 chronic stage is projected. Our analysis shows that the removal of pegylated-interferon during the acute stage of HCV infection and delaying treatment until F2 increases HCV incidence over time. The incidence will stabilize when pegylated-interferon is used as an optional treatment in the acute stage while waiting for DAA. In contrast, early treatment with DAA strongly reduces the HCV incidence over time.
S5 Fig. One-way sensitivity analysis of higher unidentified HCV reservoir

One-way sensitivity analysis of treatment immediately with DAAs after diagnosis versus delaying DAA treatment until F2 METAVIR stage with a cost-saving ICER of -€8227/QALY. In both scenarios we simulate a group of individuals with undiagnosed/untreated HCV, the so-called unidentified reservoir. We vary this group from 0-100 and 0-2000 individuals. In addition, from 2016 onwards 6500 individuals are forced into the high-risk groups of our model.

S1 Text. Model description

The model is seeded in 2002 with 3,800 HIV-infected men-who-have-sex-men (MSM) of whom 3-10% were co-infected with hepatitis C (HCV). The state variables and the HCV transmission equations are shown below. The model includes four activity $i$ based on the partner acquisition rate change: class 1 in which individuals have 20-100 HIV-infected partners per year, class 2 with 5-15 partners, class 3 with 1 -4 partners and class 4 with 0.1- 0.9 partners.

The model includes seven HCV infection stages: one stage including patients that are infected but that will clear HCV, five stages $j$ of increasing severity of fibrosis (METAVIR stages F0, F1, F2, F3, F4). Stage F4 represents cirrhosis and is sub-divided into compensated cirrhosis (F4C) and decompensated cirrhosis (F4D). Stage F0 makes a distinction between patients that are diagnosed in a timely manner and who initiated treatment, patients that are not diagnosed, patients who are diagnosed but would have cleared treatment (necessary for scenario 1 and 2), patients who refuse treatment and patients in whom treatment is delayed (necessary for the third scenario). In the model until 2015, between 67% and 75% of patients with HIV that were acutely infected with HCV were treated for 24 weeks with
pegylated interferon (PEG-IFN) and ribavirin (other patients declined treatment). Before 2012, chronically infected patients in METAVIR stages F2 through F4 were also treated with (PEG-IFN) and ribavirin. Between 2012 and 2015, boceprevir or telaprevir in addition to pegylated interferon and ribavirin, was prescribed to chronically infected patients.

After 2015, the model compares the epidemiological and economic impact of starting direct acting antivirals (DAA) immediately after HCV diagnosis, delayed until F0 chronic to await spontaneous clearance or delayed until METAVIR stage F2. When SVR is not reached the patient receives another 12 weeks of DAA treatment.

S2 Text. Technical model and equations

State variables
All individuals are MSM and infected with HIV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_i$</td>
<td>Individuals not infected with HCV; sexual activity classes $i = 1-4$</td>
</tr>
<tr>
<td>$E_i$</td>
<td>Entry rate HIV-infected MSM, sexual activity classes $i = 1-4$</td>
</tr>
<tr>
<td>$SP_i$</td>
<td>Individuals not infected with HCV that previously cleared HCV or were cured from HCV; sexual activity classes $i = 1-4$</td>
</tr>
<tr>
<td>$C_{li,n}$</td>
<td>HCV-infected individuals that are clearing HCV; sexual activity classes $i = 1-4$</td>
</tr>
<tr>
<td></td>
<td>Different forms of clearing $n$</td>
</tr>
<tr>
<td></td>
<td>1= clearing the virus and on treatment</td>
</tr>
<tr>
<td></td>
<td>2= clearing the virus and no treatment</td>
</tr>
<tr>
<td></td>
<td>3= clearing the virus and no diagnosis</td>
</tr>
<tr>
<td></td>
<td>4 = clearing the virus before diagnosis</td>
</tr>
<tr>
<td></td>
<td>B= after being infected</td>
</tr>
<tr>
<td>$F_{i,j,m}$</td>
<td>Stage of HCV infection; sexual activity classes $i = 1-4$; stage of fibrosis $j = 0-4$; $m$ is only defined for stage F0 ($j=0$) and stage F4 ($j=4$). At stage F0, $m=1$ are patients that will be treated during the acute stage and $m=2$ are patients that will not be treated. $m=3$ are patients that are not diagnosed. At stage F4, $m=1$ is compensated cirrhosis and $m=2$ decompensated cirrhosis. $R=$reinfected</td>
</tr>
<tr>
<td>$R_{xi,j,m,z}$</td>
<td>Patients receiving antiviral treatment for HCV; sexual activity classes $i = 1-4$; stage of fibrosis $j=0-4$; consecutive number of DAA courses $z$ used to treat a particular HCV infection $z=1-3$ (the value for $z$ is set to zero after cure). At stage F4, $m=1$ is compensated cirrhosis and $m=2$ decompensated cirrhosis</td>
</tr>
<tr>
<td>$N_{i,j,z}$</td>
<td>Patients in whom treatment with DAA's did not result in a sustained virological response; sexual activity classes $i = 1-4$; stage of fibrosis $j=0-4$; $z$ is number of consecutive DAA courses that were unsuccessfully used to treat HCV $z=2-3$</td>
</tr>
<tr>
<td>$C_{im}$</td>
<td>Patients with cirrhosis that are not infected with HCV, sexual activity classes $i = 1-4$, $m=1$ reflects compensated cirrhosis, $m=2$ decompensated cirrhosis</td>
</tr>
<tr>
<td>HCC</td>
<td>The occurrence of a hepatocellular carcinoma over time</td>
</tr>
</tbody>
</table>
### Input variables
The values for the input variables are given in table 1 of the main text.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_i$</td>
<td>Force of infection or the rate by which individuals become infected with HCV in sexual activity group $i$ ($i=1-4$)</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Mortality</td>
</tr>
<tr>
<td>$\mu_{\text{comp}}$</td>
<td>Mortality, compensated cirrhosis</td>
</tr>
<tr>
<td>$\mu_{\text{decomp}}$</td>
<td>Mortality, decompensated cirrhosis</td>
</tr>
<tr>
<td>$1/\tau$</td>
<td>Time to HCV clearance</td>
</tr>
<tr>
<td>$\text{SVR}_j$</td>
<td>Sustained Virological Response (SVR) in fibrosis stage of infection $j$ ($j$ is 1-4)</td>
</tr>
<tr>
<td>$\text{SVR}_{\text{PEG}}$</td>
<td>Sustained Virological Response (SVR) for acutely infected patients that received treatment with pegylated interferon (only in the scenario’s where DAAs are delayed until stage F2 or stage F3) during calibration</td>
</tr>
<tr>
<td>$\delta_j$</td>
<td>Duration of DAA treatment in stage of fibrosis $j$</td>
</tr>
<tr>
<td>$\delta_{\text{PEG}}$</td>
<td>Duration of pegylated interferon (only in the scenario’s where DAAs are delayed until stage F2 or stage F3) during calibration</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Proportion diagnosed with HCV</td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Proportion receiving treatment in acute stage of infection $E=0$ in delayed F2 scenario</td>
</tr>
<tr>
<td>Clear</td>
<td>Proportion clearing HCV</td>
</tr>
<tr>
<td>$\Theta_z$</td>
<td>Time to start the $z$th course of DAA treatment; $z=1, 2, 3$</td>
</tr>
<tr>
<td>$\Delta_{j, j+1}$</td>
<td>HCV progression rate by stage $j=0-4$</td>
</tr>
<tr>
<td>$\Delta_{\text{decomp}}$</td>
<td>Progression rate from compensated to decompensated cirrhosis</td>
</tr>
<tr>
<td>$\chi$</td>
<td>Percentage of patients that will develop an HCC over time</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Period to await spontaneous clearance to occur</td>
</tr>
</tbody>
</table>
Model equations

\[
\frac{dS_i}{dt} = E_i - S_i \times (\lambda_i + \mu)
\]

\[
\frac{dSPI}{dt} = \tau \times (CL_{i,2} + CL_{i,2B} + CL_{i,13} + CL_{i,3B} + \text{Clear}) + \delta_1 \times (CL_{i,1B} + CL_{i,1}) + \sum_{j=0}^{3} \sum_{z=1}^{2} Rx_{ij,z} \times \text{SVR}_j 
\]

\[
* \delta_j + Rx_{i,3,3} \times \delta_j \times \text{SVR}_j - Sp_i \times (\lambda_i + \mu)
\]

\[
\frac{dCl_{in}}{dt} = \text{Clear} \times \varphi \times \lambda_i \times S_i \times \epsilon - CL_{i,13} \times \varphi \times \epsilon - CL_{i,1} \times (\tau + \mu)
\]

The following equations differ per scenario

1) immediate scenario

\[
\frac{dF_{i,0,1}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times S_i + F_{i,0,3} \times \varphi \times \epsilon - F_{i,0,1} \times (\theta_z + \Delta_{0,1} + \mu)
\]

\[
\frac{dF_{i,0,1r}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times SP_i - F_{0\text{Reinf}} \times (\theta_z + \Delta_{0,1} + \mu)
\]

2) the chronic treatment scenario

\[
\frac{dF_{i,0,1}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times S_i + F_{i,0,3} \times \varphi \times \epsilon - F_{i,0,1} \times (\theta_z + \Delta_{0,1} + \mu)
\]

\[
\frac{dF_{i,0,1r}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times SP_i - F_{0\text{Reinf}} \times (\theta_z + \Delta_{0,1} + \mu)
\]

3) the delayed F2 scenario

\[
\frac{dF_{i,0,1}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times S_i + F_{i,0,3} \times \varphi \times \epsilon - F_{i,0,1} \times (\Delta_{0,1} + \mu)
\]

\[
\frac{dF_{i,0,1r}}{dt} = \varphi \times \epsilon \times (1 - \text{Clear}) \times \lambda_i \times SP_i - F_{0\text{Reinf}} \times \Delta_{0,1} + \mu
\]

\[
\frac{dF_{i,1}}{dt} = (F_{i,0,1} + F_{i,0,2} + F_{i,0,3r} + F_{i,0,3}) \times \Delta_{0,1} - F_{i,1} \times (\Delta_{1,2} + \mu)
\]

\[
\frac{dRx_{ij,z}}{dt} = F_{ij} \times \theta_z + N_{ij,z} \times \rho - Rx_{ij} \times (\delta_j + \mu) \text{ for } j = \{2,3\}, z = \{1,2\}
\]

\[
\frac{dN_{ij,z}}{dt} = Rx_{ij,z-1} \times \delta_j \times (1 - \text{SVR}_j) + N_{ij-1,z} \times \Delta_{j-1,j} - N_{ij,z} \times (\Delta_{j+1} + \theta_z + \mu) \text{ for } j = \{2,3\}, z = 2
\]
Continuation of the model equations for all scenarios

* For the delayed F2 scenario this formula is stated at the delayed F2 section

\[
\frac{dF_{i,0,2}}{dt} = (1 - \text{Clear}) * (1 - \varepsilon) * \varphi * \lambda_i * (S_i + SP_i) + F_{i,0,3} * \varphi * (1 - \varepsilon) - F_{i,0,2} * (\Delta_{0,1} + \mu)
\]

\[
\frac{dF_{i,0,3}}{dt} = (1 - \text{Clear}) * (1 - \varepsilon) * \lambda_i * (S_i + SP_i) - F_{i,0,1} * \varphi - F_{i,0,3} * (\Delta_{0,1} + \mu)
\]

\[
\frac{dF_{i,1}}{dt} = (F_{i,0,1} + F_{i,0,2} + F_{i,0,3}) * \Delta_{0,1} - F_{i,1} * (\theta_z + \Delta_{1,2} + \mu)
\]

\[
\frac{dF_{i,j}}{dt} = F_{i,j-1} * \Delta_{j-1,j} - F_{i,j} * (\theta_z + \Delta_{j+1} + \mu) \text{ for } j = \{2,3\}
\]

\[
\frac{dF_{i,4,1}}{dt} = F_{i,3} * \Delta_{3,4} - F_{i,4,1} * (\theta_z + \Delta_{\text{decomp}} + \mu_{\text{comp}})
\]

\[
\frac{dF_{i,4,2}}{dt} = F_{i,4,1} * \Delta_{\text{decomp}} - F_{i,4,2} * (\theta_z + \mu_{\text{decomp}})
\]

\[
\frac{dR_{i,j,z}}{dt} = F_{i,j} * \theta_z + N_{i,j,z} * \rho - R_{x_{i,j}} * (\delta_j + \mu) \text{ for } j = \{0,1,2,3\}, z = \{1,2\}
\]

\[
\frac{dR_{i,3,3}}{dt} = N_{i,3,2} * \theta_z - R_{x_{i,3,3}} * (\delta_j + \mu)
\]

\[
\frac{dR_{i,4,1,z}}{dt} = F_{i,4,1} * \theta_z + N_{i,4,1,z} * \theta_z - R_{x_{i,4,1}} * (\delta_j + \mu_{\text{comp}})
\]

\[
\frac{dR_{i,4,2,z}}{dt} = F_{i,4,2} * \theta_z + N_{i,4,2,z} * \theta_z - R_{x_{i,4,2}} * (\delta_j + \mu_{\text{decomp}})
\]

\[
\frac{dn_{i,j,z}}{dt} = R_{x_{i,j,z-1}} * \delta_j * (1 - \text{SVR}_j) - N_{i,j,z} * (\Delta_{j+1} + \theta_z + \mu) \text{ for } j = 0, z = 2
\]

\[
\frac{dn_{i,j,z}}{dt} = R_{x_{i,j,z-1}} * \delta_j * (1 - \text{SVR}_j) + N_{i,j-1,z} * \Delta_{j-1,j} - N_{i,j,z} * (\Delta_{j+1} + \theta_z + \mu) \text{ for } j = \{1,2,3\}, z = 2
\]

\[
\frac{dn_{i,3,3}}{dt} = R_{x_{i,3,3}} * \delta_j * (1 - \text{SVR}_j) + N_{i,3,3} * (\Delta_{3,4} + \theta_z + \mu)
\]

\[
\frac{dn_{i,4,1,z}}{dt} = R_{x_{i,4,1,z-1}} * \delta_j * (1 - \text{SVR}_j) + N_{i,4,1,z} * \Delta_{3,4} - N_{i,4,1,z} * (\Delta_{\text{decomp}} + \theta_z + \mu_{\text{comp}}) \text{ for } z = \{2,3\}
\]

\[
\frac{dn_{i,4,2,z}}{dt} = R_{x_{i,4,2,z-1}} * \delta_j * (1 - \text{SVR}_j) + N_{i,4,1,z} * \Delta_{\text{decomp}} - N_{i,4,1,z} * (\theta_z + \mu_{\text{decomp}}) \text{ for } z = \{2,3\}
\]

\[
\frac{dC_{i,1}}{dt} = \sum_{z=1}^{3} R_{x_{i,4,1,z}} * (\delta_j + \text{SVR}_j) - C_{i,1} * \mu_{\text{comp}}
\]

\[
\frac{dC_{i,2}}{dt} = \sum_{z=1}^{3} R_{x_{i,4,2,z}} * (\delta_j + \text{SVR}_j) - C_{i,2} * \mu_{\text{decomp}}
\]

\[
\frac{dC_{i,1B}}{dt} = \text{Clear} * \varphi * e * \lambda_i * \text{Spi} + C_{i,3B} * \varphi * e - C_{i,1B} * (\tau + \mu)
\]

\[
\frac{dC_{i,2}}{dt} = \text{Clear} * \varphi * (1 - e) * \lambda_i * \text{Si} + C_{i,3} * \varphi * (1 - e) - C_{i,2} * (\tau + \mu)
\]
\[
\frac{dC_{i_{2B}}}{dt} = \text{Clear} \times \phi \times (1-\epsilon) \times \lambda_i \times SP_i + Cl_{i_{1B}} \times \phi \times (1-\epsilon) - Cl_{i_{2B}} \times (\tau + \mu)
\]

\[
\frac{dC_{i_{3}}}{dt} = \text{Clear} \times \phi \times (1-\epsilon) \times Si + Cl_{i_{1}} \times \phi - Cl_{i_{3}} \times (\tau + \mu)
\]

\[
\frac{dC_{i_{3B}}}{dt} = \text{Clear} \times \phi \times (1-\epsilon) \times SP_i + Cl_{i_{3B}} \times \phi - Cl_{i_{3B}} \times (\tau + \mu)
\]

\[
\frac{dC_{i_{4}}}{dt} = \text{Clear} \times \lambda_i \times (Si + SP_i) - Cl_{i_{4}} \times (\tau + \mu)
\]

\[
\frac{dHCC}{dt} = \chi \times \sum_{j=1}^{i=4} \sum_{m=1}^{j=4} \sum_{z=1}^{m=2} F_{i,j,m} + \chi \times \sum_{j=1}^{i=4} \sum_{m=1}^{j=4} \sum_{z=1}^{m=2} R_{x_i,j,m,z} + \chi \times \sum_{j=1}^{i=4} \sum_{m=1}^{j=4} \sum_{z=1}^{m=2} N_{i,j,m,z}
\]

**Force of infection**

The equation for the force of infection includes a mixing matrix \(M_{ij}\) for infected individuals. The elements of the matrix are \(i,j\) and represent the probability that an individual with \(i\) new partnerships per year will form a new partnership with a member who has \(j\) new partners. The rate at which the sexual partner changes for individuals in each sexual activity group \(i\) is expressed as \(C_{i} \times N_{i}\). The values of the mixing matrix depend on the degree of mixing \(\epsilon\). This degree can be fully assortative \((\epsilon=1)\), where partnerships are only formed within the same activity class. Or fully random \((\epsilon=0)\) where partnerships are formed between different activity classes\(^{36,125}\).

\[
M_{ij} = \epsilon \delta + \frac{(1-\epsilon)C_{jN}\delta}{\sum_{i=1}^{i=4} \sum_{j=1}^{j=4} \sum_{m=1}^{m=2} \sum_{z=1}^{z=2} C_{iN}}
\]

Where \(\delta\) is Kronecker’s delta, with \(\delta = 1\) when \(i = j\), and \(\delta = 0\) when \(i \neq j\). The force of infection \((\lambda)\) is calculated using the following formula:

\[
\lambda_i = \lambda_{i1} \times (Cl_{i_{1},j,m} + Cl_{i_{1},m} + Cl_{i_{1},4,m} + ...)
\]

In which \(\lambda\) is the force of infection due to contact with an infected person. Similarly, \(\lambda_{i1}\) is the force of infection due to contact with one person that is infected with HCV and not on treatment.
TARGETED HCV CORE ANTIGEN MONITORING AMONG HIV-INFECTED MEN-WHO-HAVE-SEX-WITH-MEN IS COST-SAVING
Abstract

Introduction: The World Health Organization declared the goal of hepatitis C virus (HCV) elimination by 2030. Micro-elimination, which is the reduction of incidence to zero in targeted populations, is less complex and costly and may be the first step to prove whether elimination is feasible. A suitable target group are HIV-infected men who have sex with men (MSM) because of their high-risk behavior and high incidence rates. Moreover, HCV monitoring is integrated in HIV care. The current HCV monitoring approach is suboptimal and complex and may miss new HCV infections. Alternative monitoring strategies, based on alanine aminotransferase, HCV-PCR and HCV-core antigen (HCV-cAg), combined with immediate direct-acting antiviral (DAA) treatment, may be more effective in reducing new HCV infections.

Methods: A deterministic mathematical transmission model was constructed representing the Dutch HCV epidemic among HIV-infected MSM to compare different HCV monitoring strategies from 2018 onwards. We evaluated the epidemiological impact of alternative and intensified monitoring in MSM with HCV. In addition, the cost-effectiveness was calculated over a lifetime horizon.

Results: Current HCV monitoring and treatment is projected to result in an incidence of 1.1/1000 person-years, 0.24% prevalence, at a cost of €61.8 million (interquartile range 52.2–73.9). Compared with current monitoring, intensified monitoring will result in a maximum 27% reduction of incidence and 33% in prevalence at an increased cost. Conversely, compared with current monitoring, targeted HCV-cAg monitoring will result in a comparable incidence (1.1/1000 person-years) and prevalence (0.23%) but will be €1 million cheaper with increased quality-adjusted life year.

Conclusion: Targeted monitoring reduces the HCV epidemic in a cost-saving manner; however, micro-elimination may not be obtained by 2030, highlighting the need for harm-reduction programs.
Introduction

Since the introduction of well-tolerated direct acting antivirals (DAAs), the outcome of hepatitis C virus (HCV) treatment has dramatically improved. DAA treatment has a 90-95% sustained virological response (SVR) which is associated with reduced morbidity.7,8 Since cured individuals cannot transmit HCV, DAAs may be used as prevention strategy. This was shown in the Netherlands where new HCV infections among HIV-infected men-who-have-sex-with-men (MSM) were reduced by 51% after widespread DAA use in 2015.58,126

The World Health Organization (WHO) shares the optimism of DAAs as a treatment as prevention tool and declared the ambitious target of ending HCV as a public health threat in 2030.4 To achieve the 2030 elimination goals, a 90% reduction in new infections, a 90% diagnosis rate, and a 65% mortality reduction must be obtained. Micro-elimination, which is the reduction of HCV incidence to zero in targeted populations, can be used as a first step towards elimination since it is less complex and less costly.127 A suitable group for micro-elimination are HIV-infected MSM since they have high-risk behavior and are the predominant risk group for continuous HCV transmission in several high-income countries. In addition, they are a well-defined population and mostly engaged in HIV care in which HCV monitoring is integrated.68

Currently, HCV monitoring during HIV care is based on annual anti-HCV antibody tests and biannual hepatic transaminases (ALT) measurements. In addition, HCV-RNA monitoring is recommended when risk factors (e.g. ongoing injecting drug use [IDU], mucosal traumatic sex, ongoing unprotected anal intercourse and recent sexually transmitted infections) are present in combination with an unexplained elevation of ALT levels.128 Currently, guidelines advise biannual HCV-RNA or HCV core antigen (HCV-cAg) testing among HIV-infected individuals with ongoing risk factors regardless of ALT levels.128

However, the current monitoring approach has the risk of missing new HCV infections and is complex since it requires several steps and ongoing risk factors must be identified before choosing the suitable HCV monitoring approach.2,51,84 This approach also may be hampered by the fact that not all patients disclose their HCV risk factors during the HIV care appointment and that HCV-RNA monitoring is often performed with a HCV-PCR which is costly.129

To simplify the current monitoring algorithm, a direct and more sensitive HCV-PCR or HCV-cAg test can be used since no additional confirmation (one-step diagnosis), as with ALT or HCV-antibody, is needed and HCV can be detected earlier.130 Although both tests are more costly, more sensitive monitoring can be targeted to a very high-risk group to
reduce cost. Reinfections among HIV-infected MSM are common (25% to 33% within two years after cure or clearance) and associated with ongoing risk behaviour; therefore this patient population can be defined as high-risk. In this population, intensified and/or more sensitive monitoring combined with immediate DAA treatment may therefore be advantageous in reducing the number of new HCV infections.

Here, we investigated alternative monitoring strategies to intensify and simplify HCV diagnosis followed by immediate DAA treatment both among the HIV-infected MSM population and in a targeted high-risk HIV-infected MSM population in the Netherlands. In addition, we estimated the cost-effectiveness of the current guidelines and proposed monitoring strategies over a lifetime horizon.

**Methods:**

**Study design and population**
The Dutch HIV epidemic is concentrated among MSM, with nearly 70% of infected patients reporting MSM as the mode of transmission, making it very similar to the HIV epidemic in other high-income countries. The incidence rate of HCV among HIV-infected MSM is 0.6/100 persons-years. In addition, HCV reinfections are a major concern in this population and occur in 25% - 33%. The HIV epidemic is well described through a national database (ATHENA cohort), which contains anonymized clinical and demographical data of >98% of patients in HIV care in the 27 treatment centres in the Netherlands. We adapted a previously published deterministic mathematical model that represents the HCV/HIV epidemic among MSM in the Netherlands.

**Model parametrisation and calibration**
We used our previously published mathematical model representing the Dutch HIV-infected MSM epidemic which was calibrated to Dutch HIV data from the ATHENA cohort and HCV data from both Dutch Acute HCV in HIV studies (DAHHS 1 and 2). We used the estimated Dutch MSM population size, the percentage of individuals co-infected with HCV, a stable HCV incidence rate of 1.2 per 100 person-years before DAA introduction, and a stable reinfection rate of 15 per 100 PY (range 8 to 26.5 per 100 PY) (Table 1). To account for the unrestricted availability of DAAs from 2015 onwards, we validated the model's projected incidence in 2016 with the published Dutch HCV incidence data (0.4-1.0/100 person-years). Monte Carlo filtering techniques resulted in 132 out of 100,000 simulations that matched the Dutch HCV epidemic among HIV-infected MSM (Model description S1).
Our model stratifies disease progression into individuals that spontaneously clear the virus (15% - 20% of cases), three stages of progressive fibrosis (METAVIR stages F0-F3), and two stages of cirrhosis (stage F4 subdivided in compensated and decompensated cirrhosis). From stage F3, F4 compensated, and F4 decompensated cirrhosis patients can develop a hepatocellular carcinoma (HCC) with a rate of 2% - 5%.

The rate by which HCV/HIV co-infected individuals progress from a particular stage of fibrosis to a more advanced stage of fibrosis is approximately 10% per year. This rate of progression results in a probability of having cirrhosis –stage F4- of 20.8% to 48.5% after 20 to 30 years, respectively. Due to a shortage of donors, liver transplantation has not been performed in HIV/HCV co-infected individuals in the Netherlands and is therefore not considered in the model. We assumed that during HCV treatment individuals are virologically suppressed and do not transmit HCV to others. In our model before 2012, chronically infected patients in F2-F4 fibrosis stages were treated with pegylated interferon and ribavirin. Between 2012 and 2015, boceprevir or telaprevir, in addition to pegylated interferon and ribavirin, was prescribed to chronically infected patients. We assumed that until 2015, between 67% and 75% of patients were treated for 24 weeks with pegylated interferon and ribavirin (other patients declined treatment), in agreement with the treatment guidelines that were in place. Thereafter, pegylated interferon was no longer considered since DAAs were reimbursed for all stages of HCV infection in the Netherlands.

In our model there are four different risk groups in which individuals have a different number of HIV-infected partners per years (High 20-100; Medium 5-15; Medium-low 1-4; Low 0.1-0.9).

**Current HCV monitoring and DAA treatment in HIV care**

All HIV-infected MSM undergo HCV monitoring, using a biannual ALT test (hepatic transaminases) and annual antibody test in which the model assumes that approximate 85% of the HCV infections are diagnosed. In case of an elevated ALT or a positive HCV antibody test, an HCV-PCR test is used as a confirmation. After diagnosis, treatment is given immediately regardless of the possibility of clearing the infection. The model includes a median time of 18.1 weeks (range 16.5-25) from transmission until treatment initiation of acute HCV, which is based on published Dutch data on acute HCV infections. In our model all individuals who have no cirrhosis receive a 12-week DAA treatment course. SVR rates for treatment ranged from 89% to 100% with a median of 94% (Table 1). If SVR is not reached, individuals are re-treated with a 12-week DAA course. During the cirrhotic stage, DAA treatment is prolonged until 16 weeks with SVR rates for treatment of 80%-95%.

---

**Alternative HCV monitoring strategies**
<table>
<thead>
<tr>
<th>Model Parameters of HCV transmission model among Dutch MSM</th>
<th>Range/number (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual HIV diagnoses among MSM per time-period</td>
<td></td>
</tr>
<tr>
<td>2002-2014</td>
<td>720-740 (^73)</td>
</tr>
<tr>
<td>2015</td>
<td>620 (^72)</td>
</tr>
<tr>
<td>2016</td>
<td>580 (^34)</td>
</tr>
<tr>
<td>Susceptible HIV-infected MSM in 2002</td>
<td>3800 (I)</td>
</tr>
<tr>
<td>Patients with HCV in 2002</td>
<td>2-10% (^74)</td>
</tr>
<tr>
<td>Mortality rate HIV patients ≥350 CD4 count</td>
<td>1/45 (^{38})</td>
</tr>
<tr>
<td>Transmissibility of HCV</td>
<td>0.01-0.05(I)</td>
</tr>
<tr>
<td>Clearance rate</td>
<td>15-25% (^{50,66,67,85} )</td>
</tr>
<tr>
<td>Time to clearance</td>
<td>40-170 days (^{41})</td>
</tr>
<tr>
<td>Reinfection rate</td>
<td>8-26.5% per year (^{86,87} )</td>
</tr>
<tr>
<td>Time from transmission until treatment</td>
<td>16.5 - 25 weeks (^{98} )</td>
</tr>
<tr>
<td>Patients in stage F3, F4 in 2002</td>
<td>10-30% (I)</td>
</tr>
<tr>
<td>HCC rate</td>
<td>2-5% (^{89,90} )</td>
</tr>
<tr>
<td>Monitoring parameters</td>
<td>Diagnosed percentage per monitoring cycle</td>
</tr>
<tr>
<td>Biannual ALT and annual HCV antibodies</td>
<td>70-100 (^{53,84} )</td>
</tr>
<tr>
<td>HCV-PCR</td>
<td>90-100 (^{96,135} )</td>
</tr>
<tr>
<td>HCV- core antigen test</td>
<td>90-100 (^{136,137} )</td>
</tr>
<tr>
<td>Treatment parameters</td>
<td>Range/number</td>
</tr>
<tr>
<td>SVR, DAA F0-F3</td>
<td>89-100% (^{5,93} )</td>
</tr>
<tr>
<td>Treatment duration F0-F3</td>
<td>12 weeks (^{92} )</td>
</tr>
<tr>
<td>SVR, DAA cirrhosis</td>
<td>80-95% (^{93} )</td>
</tr>
<tr>
<td>Treatment duration F4 compensated and decompensated</td>
<td>16 weeks (^{94} )</td>
</tr>
<tr>
<td>Re-treatment duration F0-F3</td>
<td>12 weeks (^{92} )</td>
</tr>
<tr>
<td>Re-treatment duration F4 compensated and decompensated</td>
<td>16 weeks (^{94} )</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Utility score</td>
</tr>
<tr>
<td>HIV mono-infection</td>
<td>0.94(^{95} )</td>
</tr>
<tr>
<td>Acute HCV infection</td>
<td>0.89-0.94(^{88,95} )</td>
</tr>
<tr>
<td>HCV F0-F3 stage</td>
<td>0.89-0.94(^{95,98} )</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>0.38-0.67(^{97} )</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>0.38(^{97} )</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0.45(^{138} )</td>
</tr>
<tr>
<td>DAA based therapy</td>
<td>0.89-0.94(^{88,95} )</td>
</tr>
</tbody>
</table>
Alternative HCV monitoring strategies

From 2018 onwards, alternative monitoring strategies are simulated in the model, which we compared with the current monitoring approach described in the previous paragraph (Figure 1). In the different monitoring strategies, we replaced ALT monitoring by one-step diagnostics (no anti-HCV antibody and HCV-PCR confirmation needed) to an HCV-PCR or HCV-cAg. Both tests are more sensitive and can identify 90%-100% of patients two weeks after HCV infection; however, the HCV-cAg is less costly than the HCV-PCR (Table 1). In addition, we intensified ALT, HCV-PCR and HCV-cAg monitoring from six monthly to three, and once monthly. Since reinfection is common among HIV-infected MSM, we targeted the above-mentioned monitoring strategies solely to a group of previously HCV/HIV co-infected MSM (high-risk group), while the rest of the HIV-infected MSM is continuously monitored with ALT. Similar to the current monitoring strategy, the HCV-

**Table 1. Continued**

<table>
<thead>
<tr>
<th>Model Parameters of HCV transmission model among Dutch MSM</th>
<th>Range/number (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs</strong></td>
<td><strong>Price in €</strong></td>
</tr>
<tr>
<td>Doctors visit</td>
<td>136*</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>105-225†</td>
</tr>
<tr>
<td>HCV core antigen</td>
<td>32†</td>
</tr>
<tr>
<td>Confirmation infection (PCR price)</td>
<td>105-225†</td>
</tr>
<tr>
<td>HCV genotyping</td>
<td>130-252†</td>
</tr>
<tr>
<td>Indirect laboratory cost</td>
<td>6.47-8</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>130-252†</td>
</tr>
<tr>
<td>Ultrasound of the liver</td>
<td>90-226†</td>
</tr>
<tr>
<td>Biochemistry and liver function tests</td>
<td>38-46†</td>
</tr>
<tr>
<td>F3-F4 additional costs per year**</td>
<td>808†</td>
</tr>
<tr>
<td>DAA regimen 12 weeks</td>
<td>35,000†</td>
</tr>
</tbody>
</table>

* Successfully treated patients who achieved viral suppression and attained a CD4+ cell count of at least 350 cells/µl within 1 year of starting ART had a normal life expectancy, with a 35-year-old HIV-infected person estimated to live to about 80 years on average.

** Additional costs per year are based on the abdominal echo’s (HCC screening), additional doctor appointments and biochemistry.

¥ Weeks are based on the time that a patient needs to be diagnosed (16.5-25 weeks) with an additional number of weeks that is “waited” until a patient reach possible spontaneous clearance. In the model we “wait” an additional 3-3.5 months for spontaneously clearance (+/- 90 days).

§ The model considers the HCV/HIV co-infection utility score to be an interaction between the utility for HIV mono and HCV mono scores. The utility scores are varied in the sensitivity analysis.

† Dutch data summarized out of different academic hospitals in the Netherlands.

PCR is used as confirmation after an elevated ALT. Additionally, the HCV-PCR and HCV-cAg do not require additional confirmation (Figure 1). When monitoring is intensified, subsequently the time to treatment is shorted since DAA treatment is started immediately after diagnosis, for example, within three or one month. In the model, we assume that if an HCV infection is undiagnosed, the patient will be retested in the next period. All monitoring strategies are implemented in 2018, and HCV incidence, prevalence, and sequelae, by projecting the number of HCC avoided, are evaluated among HIV-infected MSM over a lifetime horizon of 40 years.

Costs and QALY estimates
The cost-effectiveness analysis was performed from a provider perspective. Each compartment in our deterministic model was assigned a costs and quality adjusted life year (QALY) score (Table 1). HCV monitoring and treatment costs were collected among the six Academic Medical Centres in the Netherlands. Our model used a DAA price of €35,000 for a 12-week treatment course, which is varied in the sensitivity analysis. QALY weights were obtained from data of the Dutch HIV/HCV co-infected MSM cohort (DAHHS). HIV-infected MSM have a QALY of 0.94. The model considers the HCV/HIV co-infection utility-score to be an interaction between the HIV-mono and HCV-mono infected utility scores. HCV/HIV co-infected MSM are assumed to have a utility score of 0.84 during F0-F3 stage. QALY scores during DAA treatment remained similar. After resolving the HCV infection, the QALY score returned to that of an HIV mono-infected (i.e. 0.94). Both costs and QALY scores were discounted at 3% per year. For this study, we used a willingness-to-pay threshold of €20,000 per QALY.

HIV-infected MSM are co-infected with HCV at a median age of 40 years. In addition, an HIV-infected MSM with CD4 >350 cells/µl has a life expectancy of 80 years. Therefore, we used a 40-year time horizon to calculate the epidemiological impact and economic outcomes. The reported numbers are the median values with the corresponding interquartile range between brackets. Prices are notated in euros (€).

Sensitivity analysis and uncertainties
We performed a one-way sensitivity analysis of the incremental cost-effectiveness ratios (ICER) comparing the current approach, based on monitoring with biannual ALT tests and annual HCV-antibody tests, with the strategy in which ALT is replaced with a more sensitive HCV-cAg test and targeted to the high-risk group (previously HCV/HIV co-infected MSM). Several key input variables were varied: cost of DAAs (€5,000 - €50,000), cost of a doctor appointment (increase and decrease of 50%), spontaneous clearance rate (5%-30%), discounting rates (0% – 5%), and QALY score during DAA treatment (increase and decrease of 4%). After DAA treatment a patient will return to a QALY of 0.94,
which is similar to an individual with an HIV mono-infection. In addition, we changed the price of the highly sensitive diagnostic tools (€2 - €200) (HCV-PCR and HCV-cAg) and confirmatory test (HCV-PCR).

Figure 1. Simplified schematic representation of alternative monitoring strategies in the hepatitis C transmission model

This model is based on our previously published model. The stage of fibrosis is represented by the METAVIR stage F0, F1, F2, F3, and F4. In our model 15%-20% of the patients can spontaneously clear their infection. The current monitoring strategy is indicated in the first column (left) and based on the EACS guidelines where all patients are monitored with biannual ALT tests and annual HCV-antibody tests. In the next column monitoring is either increased (time interval of three-monthly or monthly) or ALT monitoring is replaced with a more sensitive test such as the HCV-PCR or HCV-cAg among all HIV-infected MSM. In the third column the alternative monitoring strategies are targeted to the high-risk group (previously HCV/HIV co-infected MSM), while all other HIV-infected MSM follow the monitoring approach based on ALT testing (current monitoring approach). All HCV-infected individuals follow the natural course of HCV when they are not treated with direct-acting antivirals.

Abbreviations: DAA= direct-acting antivirals, HCC= hepatocellular carcinoma, HCV= hepatitis c virus, MSM= men-who-have-sex-with-men, SVR= sustained virological response

Recently, the HCV prevalence has been increasing among HIV pre-exposure prophylaxis (PrEP) users, in contrast to a stabilizing prevalence among HIV-negative MSM. In addition, literature suggests mixing of HCV between MSM with high-risk behaviour
regardless of HIV-status.\textsuperscript{77,140,141} As specific data needed for calibration of HCV among HIV-uninfected MSM and PrEP-users is not fully available, we accounted for the interaction with HIV-uninfected MSM in our sensitivity analysis. We modelled an increase in the number of MSM in the high- and medium-high-risk groups (regardless of HIV-status) who are at risk for HCV (600 since the introduction of HIV PrEP in 2015 and 6000 in 2018 to simulate an upscale).\textsuperscript{104} In addition, we accounted for the impact of continuing transmission and interaction with undiagnosed HCV-infected individuals, such as HIV-negative MSM, HIV-infected MSM not in care, and people-who-inject-drugs (PWIDs) (500 individuals per year that remain undiagnosed from 2018 onwards) combined with the influence of increasing the number of high-risk HIV-infected MSM.

Table 2. Different monitoring strategies with short-term epidemiological impact and sequelae over a lifetime horizon

<table>
<thead>
<tr>
<th>Monitoring strategies/ m= months of monitoring interval</th>
<th>Short-term HCV incidence per 1000 person-years</th>
<th>Short-term HCV prevalence (%)</th>
<th>HCC avoided over a lifetime horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current monitoring</td>
<td>1.12</td>
<td>0.24</td>
<td>15</td>
</tr>
<tr>
<td>ALT (m=3)</td>
<td>0.96</td>
<td>0.20</td>
<td>15</td>
</tr>
<tr>
<td>ALT (m=1)</td>
<td>0.85</td>
<td>0.16</td>
<td>26</td>
</tr>
<tr>
<td>HCV-core antigen (m=6)</td>
<td>1.08</td>
<td>0.23</td>
<td>1</td>
</tr>
<tr>
<td>HCV-core antigen (m=3)</td>
<td>0.92</td>
<td>0.21</td>
<td>16</td>
</tr>
<tr>
<td>HCV-core antigen (m=1)</td>
<td>0.78</td>
<td>0.20</td>
<td>26</td>
</tr>
<tr>
<td>HCV-PCR (m=6)</td>
<td>1.08</td>
<td>0.23</td>
<td>1</td>
</tr>
<tr>
<td>HCV-PCR (m=3)</td>
<td>0.92</td>
<td>0.21</td>
<td>16</td>
</tr>
<tr>
<td>HCV-PCR (m=1)</td>
<td>0.78</td>
<td>0.20</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted to the high-risk group/ m= months of monitoring interval</th>
<th>Short-term HCV incidence per 1000 person-years</th>
<th>Short-term HCV prevalence (%)</th>
<th>HCC avoided over a lifetime horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (m=3)</td>
<td>1.01</td>
<td>0.22</td>
<td>4</td>
</tr>
<tr>
<td>ALT (m=1)</td>
<td>0.91</td>
<td>0.20</td>
<td>7</td>
</tr>
<tr>
<td>HCV-core antigen (m=6)</td>
<td>1.08</td>
<td>0.23</td>
<td>1</td>
</tr>
<tr>
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<tr>
<td>HCV-PCR (m=6)</td>
<td>1.08</td>
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<td>1</td>
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<tr>
<td>HCV-PCR (m=3)</td>
<td>1.01</td>
<td>0.22</td>
<td>4</td>
</tr>
<tr>
<td>HCV-PCR (m=1)</td>
<td>0.91</td>
<td>0.20</td>
<td>7</td>
</tr>
</tbody>
</table>

Short-term epidemiological impact and long-term sequelae of HCV in the form of hepatocellular carcinomas avoided when different monitoring strategies are applied with the ALT, HCV-PCR, and HCV-cAg test. In addition, monitoring is intensified from six monthly time intervals towards three and monthly time intervals.
Results:

Our model projects that continuing the current monitoring approach, results in an incidence rate of 1.1 per 1000 person-years with a 0.24% prevalence after 20 years (Table 2).

**Impact of intensified and more sensitive monitoring strategies for all HIV-infected MSM**

Intensifying ALT monitoring with three-monthly time intervals reduces the incidence rate from 1.1 per 1000 person-years to 1.0/1000 person-years with a 0.20% prevalence after 20 years. Further intensifying monitoring with monthly time intervals reduces incidence rate to 0.9/1000 person-years with a 0.16% prevalence (Table 2). When replacing ALT monitoring by a simplified monitoring strategy based on the HCV-PCR or HCV-cAg test, our model demonstrates that six monthly monitoring results in an incidence rate of 1.1/1000 person-years and a 0.23% prevalence. With intensified monitoring similar as seen with ALT monitoring; the incidence rate declines to 0.9/1000 person-years, with a 0.19% prevalence (20% reduction) with three-monthly intervals, and to 0.8/1000 person-years, with a 0.16% prevalence (33% reduction) with monthly intervals regardless of the test method. Intensified and simplified monitoring results in a maximum of 26 HCCs averted over 20 years regardless of test used (Table 2).

**Impact of monitoring strategies targeted to a high-risk group of previously HCV/HIV co-infected MSM**

Intensifying ALT monitoring with time intervals of every three months and monthly after 20 years reduces the incidence rate to 1.0/1000 person-years with a 0.22% prevalence and to 0.9/1000 person-years with a 0.20% prevalence, respectively in a high-risk group of previously HCV/HIV co-infected MSM. When ALT monitoring is replaced by a simplified monitoring strategy based on the HCV-PCR or HCV-cAg test, our model projects an incidence rate to 1.1/1000 person-years (Table 2), with a 0.23% prevalence. With intensified monitoring, the incidence rate declines to 1.0/1000 person-years, with a 0.22% prevalence (8% reduction), and to 0.9/1000 person-years, with a 0.20% prevalence (17% reduction), when monitoring with three-monthly and monthly time intervals regardless of the test, respectively. Intensified and simplified monitoring results in a maximum of 7 HCCs averted over 20 years regardless of test used (Table 2).

**Cost-effectiveness**

Our model showed that continuing ALT- based HCV monitoring according to the current guidelines costs an overall €61.8 million (interquartile range 52.2 – 73.9) for the Dutch HCV epidemic among HIV-infected MSM over a lifetime horizon (Table 3). When
monitoring with ALT is increased, three-monthly time intervals, a more costly scenario results, that is, €64.8 million (56.2 – 73.7), among all HIV-infected MSM. Replacing the ALT test results in higher costs of €67.1 million (58.3 – 75.0) and €92.2 million (82.2 – 100.6) when monitored every three months for the HCV-cAg and HCV-PCR, respectively. In addition, the different monitoring scenarios result in a similar number of QALYs and are therefore dominated (higher cost and similar or lower number of QALYs) (Table S2).

A more targeted monitoring approach towards the high-risk group (previously HCV/HIV co-infected MSM) using the HCV-cAg, however, was less costly at, €60.7 million (51.9 – 71.6) for the total HCV epidemic among HIV-infected MSM (Table 3). Monitoring with the HCV-PCR, as recommended by the European AIDS Clinical Society guidelines for individuals with ongoing risk behaviour, was slightly more expensive at €63.5 million (56.2 – 73.7). Monitoring with both the HCV-cAg and HCV-PCR test results in an increase of 1.4 QALYs over 40 years, compared with the current monitoring approach. Since the HCV-cAg is less costly and results in an increase in QALYs this strategy is considered cost-saving. Since the HCV-PCR is more costly (€ 63.5 million) and results in a similar number of QALYs gained (1.4), this is less favourable and considered dominated. All other monitoring interventions cost more and result in a similarly number of QALYs, therefore they are either not cost-effective or dominated (Table 3, Table S2).

**Sensitivity analysis**

We performed a one-way sensitivity analysis to identify the factors that most strongly influences the cost-effectiveness ratio (Figure 2). Our results show that the ICER strongly depends on the price of the diagnostic and confirmation tool, whereas a decrease result in a more cost-saving strategy. The price of the DAAs influences the ICER to a lesser extent and monitoring with an HCV-cAg test in a high-risk group remains cost-saving with a lower DAA price of €5,000. In addition, our sensitivity analysis showed that interaction with high-risk HIV-negative MSM and an unidentified population, such as PWIDs or HIV-negative MSM not in care, increases the ICER. The ICER remains, however, cost-saving. Factors as QALYs, cost of a doctor visit, clearance and discounting had a limited impact on the cost effectiveness ratios.
Figure 2. One-way sensitivity analysis the incremental cost-effectiveness ratio (ICERs) (€/QALY)

We compared the current situation with monitoring the high-risk group with an HCV-cAg test at six monthly time intervals and varied different key parameters. The bars show the range in ICER if these key variables are varied. All ICERs are stated in euros.

### Table 3. Cost-effectiveness in incremental cost-effectiveness ratio (ICER) per alternative monitoring strategy

<table>
<thead>
<tr>
<th>Monitoring strategies (m= time interval in months)</th>
<th>HCV infections averted compared with S1 at 20 years</th>
<th>Prevalence reduction (%) at 20 years</th>
<th>Cumulative HCCs avoided over 40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current monitoring strategy (S1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV core antigen (m=6) high-risk group</td>
<td>19</td>
<td>2.8</td>
<td>1</td>
</tr>
<tr>
<td>HCV PCR (m=6) High-risk group</td>
<td>19</td>
<td>2.8</td>
<td>1</td>
</tr>
<tr>
<td>ALT (m=3) risk group</td>
<td>57</td>
<td>7.9</td>
<td>4</td>
</tr>
<tr>
<td>HCV core antigen (m=1) high-risk group</td>
<td>124</td>
<td>15.5</td>
<td>7</td>
</tr>
</tbody>
</table>

This table shows the short-term epidemiological impact, long term sequelae (cumulative avoided hepatocellular carcinomas (HCCs)) and cost-effectiveness over a lifetime horizon of 40 years. The incremental cost-effectiveness ratio (ICER) is calculated based on the incremental cost and incremental QALYs of the previous less costly scenario. If the incremental QALYs are equal or lower the ICER is dominated. Costs and QALYs are calculated over a lifetime horizon of 40 years. A willingness-to-pay threshold of €20,000 is considered. Monitoring strategies as increased (three-monthly and monthly) monitoring among all HIV-infected MSM, HCV-PCR and HCV-cAg monitoring among all HIV-infected MSM, increased (monthly and three-monthly) monitoring with the HCV-PCR and HCV-cAg among all HIV-infected MSM, are dominated, for the full figure see supplement (table S2).

### Discussion:

We used mathematical modelling to compare the impact of alternative HCV monitoring strategies on the HCV epidemic among HIV-infected MSM in the Netherlands. Alternative monitoring strategies, that is, intensified ALT monitoring or monitoring with an HCV-PCR or HCV-cAg test, in all HIV-infected MSM results in a decrease of incidence and prevalence but will cost more. A targeted HCV-cAg monitoring strategy aimed only at a high-risk population of previously HCV/HIV co-infected MSM, not only reduces the incidence and prevalence but is also less costly compared with the current monitoring approach. Therefore, monitoring with the HCV-cAg in a targeted population of high-risk individuals is cost-saving.

This is the first study that modelled alternative monitoring strategies in a group of HIV-infected MSMs. In addition this is the first study in which more sensitive and simplified monitoring was targeted to previously HCV/HIV co-infected MSM with the hypothesis of a higher risk of HCV infection due to high-risk behaviour (reinfection rates are 25%-33%). Currently, guidelines advise the use of a more sensitive diagnostic test, with the possibility of earlier HCV detection compared with ALT monitoring and anti-HCV antibodies, when
Table 3. Cost-effectiveness in incremental cost-effectiveness ratio (ICER) per alternative monitoring strategy

<table>
<thead>
<tr>
<th>Monitoring strategies (m= time interval in months)</th>
<th>HCV infections averted compared with S1 at 20 years</th>
<th>Prevalence reduction (% at 20 years)</th>
<th>Cumulative HCCs avoided over 40 years</th>
<th>Lifetime costs of the HCV epidemic among HIV-infected MSM per million (€)</th>
<th>Lifetime QALY x 1000</th>
<th>Incremental cost (a) € x 1000</th>
<th>Incremental QALYs (b)</th>
<th>ICER (a/b) x 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current monitoring strategy (S1)</td>
<td>61.8(52.2–73.9)</td>
<td>357.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV core antigen (m=6) high-risk group</td>
<td>19</td>
<td>2.8</td>
<td>1</td>
<td></td>
<td>60.7(51.9–71.6)</td>
<td>-649</td>
<td>1.43</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>HCV PCR (m=6) High-risk group</td>
<td>19</td>
<td>2.8</td>
<td>1</td>
<td></td>
<td>63.5(54.7 –100.9)</td>
<td>2,900</td>
<td>0</td>
<td>Dominated*</td>
</tr>
<tr>
<td>ALT (m=3) risk group</td>
<td>57</td>
<td>7.9</td>
<td>4</td>
<td></td>
<td>64.8(56.2–73.7)</td>
<td>4,025</td>
<td>2.12</td>
<td>1,976</td>
</tr>
<tr>
<td>HCV core antigen (m=1) high-risk group</td>
<td>124</td>
<td>15.5</td>
<td>7</td>
<td></td>
<td>93.6(84.9-101.0)</td>
<td>27,472</td>
<td>2.92</td>
<td>9,153</td>
</tr>
</tbody>
</table>

This table shows the short-term epidemiological impact, long-term sequelae (cumulative avoided hepatocellular carcinomas (HCCs)) and cost-effectiveness over a lifetime horizon of 40 years. The incremental cost-effectiveness ratio (ICER) is calculated based on the incremental cost and incremental QALYs of the previous less costly scenario. If the incremental QALYs are equal or lower the ICER is dominated.*

Costs and QALYs are calculated over a lifetime horizon of 40 years. A willingness-to-pay threshold of €20,000 is considered. Monitoring strategies as increased (three-monthly and monthly) monitoring among all HIV-infected MSM, HCV-PCR and HCV-cAg monitoring among all HIV-infected MSM, increased (monthly and three-monthly) monitoring with the HCV-PCR and HCV-cAg among all HIV-infected MSM, are dominated, for the full figure see supplement (table S2).

*Dominated; when the compared strategy has equal or less QALYs compared with the previous less costly scenario

Abbreviations; HCC= hepatocellular carcinoma, HCV= hepatitis C, HCV-cAg= HCV core antigen, S1= current monitoring approach based on ALT monitoring

Discussion:

We used mathematical modelling to compare the impact of alternative HCV monitoring strategies on the HCV epidemic among HIV-infected MSM in the Netherlands. Alternative monitoring strategies, that is, intensified ALT monitoring or monitoring with an HCV-PCR or HCV-cAg test, in all HIV-infected MSM results in a decrease of incidence and prevalence but will cost more. A targeted HCV-cAg monitoring strategy aimed only at a high-risk population of previously HCV/HIV co-infected MSM, not only reduces the incidence and prevalence but is also less costly compared with the current monitoring approach. Therefore, monitoring with the HCV-cAg in a targeted population of high-risk individuals is cost-saving.

This is the first study that modelled alternative monitoring strategies in a group of HIV-infected MSM. In addition this is the first study in which more sensitive and simplified monitoring was targeted to previously HCV/HIV co-infected MSM with the hypothesis of a higher risk of HCV infection due to high-risk behaviour (reinfection rates are 25%-33%). Yet, previously infected patients have a higher risk of reinfection. Our model projected that a more stratified approach among previously HCV-infected individuals resulted in a reduction of the overall cost of the HCV epidemic among HIV-infected MSM, despite the use of a more costly diagnostic test compared with ALT monitoring.

Moreover, a more sensitive test, such as the HCV-PCR or HCV-cAg test, not only results in early diagnosis of HCV but also accelerates the result and simplifies HCV monitoring. While elevated ALT or a positive anti-HCV antibody requires additional confirmation, an HCV-PCR or HCV-cAg is a one-step approach. One step-diagnostics are beneficial to avoid losing patients out of the HCV care cascade. This is less likely for HIV-infected MSMs, who are integrated in HIV care, but more essential to other risk groups as HIV-uninfected MSM or PWIDs. In addition, a more sensitive monitoring approach is more feasible compared with intensified monitoring since the latter requires additionally hospital appointments.
The results of this study are of importance since the WHO recommends using cost-effectiveness analysis to determine the best value for money. In addition, there is a lack of financial resources towards testing and treatment of HCV.\textsuperscript{4,9} In the past years most focus has been on the cost of DAAs and the cost-effectiveness of DAAs while little focus has been put on the cost and cost-effectiveness of diagnostics. Still, many individuals are unaware of their HCV infection, and test and treat in high-risk population showed tremendous epidemiological and cost benefits.\textsuperscript{9,126} Our model showed that when monitoring is targeted properly to the right risk groups, cost can be avoided, and benefits are gained.

To diagnose 90% of the individuals with a chronic HCV infections by 2030, a target of the WHO, it is important to assess the price of the diagnostic test.\textsuperscript{4} Currently, the HCV-PCR is more costly (€105-€225) compared with the HCV-cAg test (€32), but both tests have a similar performance.\textsuperscript{136,137} Therefore, the HCV-cAg test can play a significant role in HCV diagnostic in high-income settings, because it has a more affordable price and similar performance to the HCV-PCR. Moreover, our model showed that HCV-PCR monitoring in a high-risk group, as recommended by the guidelines, is not cost-effective, based on the current HCV-PCR pricing.\textsuperscript{128} Nevertheless, the current overall price of HCV-diagnostics is very costly for many countries, especially in low- and middle-income countries, where huge numbers require HCV screening and monitoring.

In the Netherlands, HCV incidence among HIV-infected MSM already declined significantly after unrestricted access to DAA treatment.\textsuperscript{58,126} Therefore, the next step towards the WHO elimination goal is HCV micro-elimination in the HIV-infected MSM population, the major transmitters of new HCV infections in the Netherlands.\textsuperscript{48,55,56} Consequently, the impact of intensified testing is rather small. Unfortunately, our model showed that, even with monthly HCV monitoring followed by immediate DAA treatment, micro-elimination in this population is not obtained by 2030. Another modelling study from Salazar-Vízcaraya et al. showed that risk-reduction in combination with an upscale of DAA treatment could result in micro-elimination.\textsuperscript{115} Our model also indicated that a reduction in risk behaviour is needed to reach elimination by 2030 (data not shown). This information highlights the need for harm reduction programs in the HIV-infected MSM population.

A key strength of our model is that we have access to data of the well monitored Dutch HIV epidemic and that we could calibrate our data to new HCV diagnoses among people living with HIV in the Netherlands.\textsuperscript{58,72} Therefore, our model is calibrated to complete and accurate data on the annual number of (newly) diagnosed HIV-infected MSM, which allows us to make accurate predictions on the epidemiological effect of alternative monitoring strategies and the possibility of achieving micro-elimination.\textsuperscript{126}
Our model has several limitations. First, since specific data, regarding HCV transmission and interaction of HCV with HIV-negative MSM, was not available, our model considered only HCV transmission among HIV-infected MSM, although HCV transmission is found less frequently among HIV-negative MSM. HIV pre-exposure prophylaxis (PrEP) usage could increase HCV incidence, as reported by some studies. This could result in expansion of HCV among HIV-uninfected MSM, with high-risk behavior. Therefore, we accounted for the effect of interaction between the HIV-infected MSM and HIV-uninfected MSM population in our sensitivity analysis. This shows that regardless of an increased HCV incidence in the HIV-uninfected population, HCV-cAg monitoring in a high-risk population remains cost-saving. Second, data regarding the number of individuals who acquire HCV outside the Netherlands are limited. In addition, interaction with populations whom are not in care, for example PWIDs or “illegal” PrEP users might result in new HCV infections among HIV-infected MSM. To account for interaction with an unidentified and untreated population (transmission outside the Netherlands, PWIDs and “illegal” PrEP users) we conducted a sensitivity analysis that showed an a cost increase but remained a cost-saving strategy.

Conclusion

Our model showed that the HCV epidemic among HIV-infected MSM can be reduced in a cost-saving manner by simplifying monitoring strategies using targeted one-step diagnostics with the HCV-cAg. However, since we are reaching towards elimination the epidemiological impact is rather small. Nevertheless, the HCV-cAg test can play a significant role in HCV diagnostic in high-income settings because it has an affordable price and similar performance to the HCV-PCR. In addition, in the past years most focus has been on the cost of DAAs and very little focus has been placed on the cost of diagnostics. Currently, using an HCV-PCR when risk factors are present, as recommended by the guidelines, is not cost-effective because HCV-PCR pricing is high. Therefore, the next step towards elimination is to simplify diagnostics and lower the prices of diagnostic tools. Unfortunately, despite intensified monitoring strategies our model does not predict micro-elimination of HCV before 2030 and indicates the need for harm reduction programs.
Supporting information

S1 Model description and calibration
The model is seeded in 2002 with 3,800 HIV-infected men-who-have-sex-men (MSM) of whom 3-10% were co-infected with hepatitis C (HCV). The state variables are described in table 1. All HCV transmission equations are described in “Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men” Popping S et al. 2019 PLOS ONE 14(1): e0210179. https://doi.org/10.1371/journal.pone.0210179. Our model includes four activity groups based on the partner acquisition rate change per year: class 1 (high) in which individuals have 20-100 HIV-infected partners per year, class 2 (medium) with 5-15 partners, class 3 (medium – low) with 1-4 partners and class 4 (low) with 0.1-0.9 partners.

The model includes seven HCV infection stages: one stage including patients that are infected but that will clear HCV, five stages of increasing severity of fibrosis (METAIR stages F0, F1, F2, F3, F4). Stage F4 represents cirrhosis and is sub-divided into compensated cirrhosis (F4C) and decompensated cirrhosis (F4D). Stage F0 makes a distinction between patients that are diagnosed in a timely manner and who initiated treatment, patients that are not diagnosed, patients who are diagnosed but would have cleared treatment, and patients who refuse treatment. In addition, the model accounts for the cost of overtreatment of patients who are put on treatment but would have cleared their infection.

Patients are monitored in the model when they are in the susceptible stage, considered susceptible (infection is not diagnosed, due to a false negative test), susceptible after a previous HCV infection, and considered susceptible after a previous HCV infection. HCV monitoring is performed with several tests, HCV-antibodies, ALT, HCV-PCR, and the HCV-core antigen depending on the scenario. In addition, monitoring intervals vary from every six months, every three months, and monthly. We targeted monitoring interventions to a high-risk group of patients who previously were infected with HCV, while all other HIV-infected MSM are monitored with biannual ALT measurements and HCV-antibodies. As soon as a patient is diagnosed DAA treatment is started.

Treatment is calibrated as followed; in the model until 2015, between 67% and 75% of patients with HIV that were acutely infected with HCV were treated for 24 weeks with pegylated interferon (PEG-IFN) and ribavirin (other patients declined treatment). Before 2012, chronically infected patients in METAIR stages F2 through F4 were also treated with (PEG-IFN) and ribavirin. Between 2012 and 2015, boceprevir or telaprevir in addition to pegylated interferon and ribavirin, was prescribed to chronically infected
patients. In 2015 unrestricted DAAs became available and we calibrated to this effect, using the Dutch incidence rates in 2016. From 2018 onwards, the model compares the epidemiological and economic impact of different monitoring strategies as described in the previous paragraph.

Table S2. Outcome cost-effectiveness analysis

<table>
<thead>
<tr>
<th>Monitoring strategies</th>
<th>Lifetime costs per million (€)</th>
<th>Lifetime QALY x 1000</th>
<th>ICER (a/b) x 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current monitoring strategy (S1)</td>
<td>61.8(52.2–73.9)</td>
<td>358</td>
<td></td>
</tr>
<tr>
<td>HCV-core antigen(t=6) risk group</td>
<td>61.0(52.2–72.8)</td>
<td>358</td>
<td>Cost-saving</td>
</tr>
<tr>
<td>HCV-PCR (t=6) risk group</td>
<td>63.8(55.1 -75.7)</td>
<td>358</td>
<td>Dominated*</td>
</tr>
<tr>
<td>ALT (t=3) risk group</td>
<td>64.8(56.2–73.7)</td>
<td>358</td>
<td>1,689</td>
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<tr>
<td>HCV-core antigen(t=3) risk group</td>
<td>67.1(58.3-75.0)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-core antigen (t=6)</td>
<td>68.3(59.9-80.8)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>ALT (t=1) risk group</td>
<td>88.4(79.5-95.6)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-PCR (t=3) risk group</td>
<td>92.2(82.2-100.6)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-core antigen(t=1) risk group</td>
<td>93.8(85.3-101.5)</td>
<td>358</td>
<td>9,239</td>
</tr>
<tr>
<td>HCV-PCR (t=6)</td>
<td>121.8(114.1-134.0)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-PCR (t=1) risk group</td>
<td>165.5(156.4-178.1)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>ALT (t=3)</td>
<td>169.6(163.5-175.9)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-core antigen (t=3)</td>
<td>216.1(210.1-223.8)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>ALT (t=1)</td>
<td>650.0(645.3-655.1)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-PCR (t=3)</td>
<td>688.9(682.4-695.7)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-core antigen (t=1)</td>
<td>761.6(756.6-758.4)</td>
<td>358</td>
<td>Dominated</td>
</tr>
<tr>
<td>HCV-PCR (t=1)</td>
<td>2,180(2,175-2,186)</td>
<td>358</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

Dominated; when the compared strategy has equal or less QALYs compared with the previous less costly scenario
Part 2
5
THE NEED FOR A EUROPEAN HEPATITIS C PROGRAM MONITORING RESISTANCE TO DIRECT ANTIVIRAL AGENTS IN REAL-LIFE TO ELIMINATE HEPATITIS C

Stephanie Popping, Valeria Cento, Federico García, Francesca Ceccherini-Silberstein, Carole Seguin-Devaux, David van de Vijver, Charles Boucher; on behalf of the HEPVIR working group of the European Society for translational antiviral research (ESAR)

Abstract:

The World Health Organization (WHO) has declared that hepatitis C virus (HCV) should be eliminated as a public health threat. A key recommendation to reach this elimination goal, is to reduce new infections by 90% and liver-related mortality by 65%. Highly effective direct antiviral agents (DAA) play a major role in this elimination. Unfortunately, DAA treatment fails approximately 2.5% - 5% of the patients, often in the presence of resistance associated substitutions (RAS). This could eventually lead to a total number of 1.8 - 3.6 million first line DAA failures. RAS may jeopardize the elimination goals for several reasons; most importantly, virus transmission and infection progression will continue. More data are required to handle RAS adequately and identify mutational patterns causing resistance. Currently, sample sizes are small, data are scattered and methods heterogenic. Collaboration is therefore key and a European collaboration, such as HEPCARE, should provide a solution.
Viewpoint

Currently, it is estimated that 71 million people are living with hepatitis C (HCV). The World Health Organization (WHO) has declared that HCV could be eliminated as a public health threat by 2030. A key recommendation to reach this elimination goal, is reducing new infections by 90% and HCV related liver-mortality by 65%.

Different strategies can be used to reduce HCV transmission, for example are blood screening, injection safety, and harm reduction programs. In Europe, blood screening and injection safety already substantially declined HCV transmission. The introduction of direct-acting antivirals (DAAs), however, seemed a more promising tool to reach elimination. DAAs provide excellent treatment owing to high cure rates and limited side-effects. Moreover, DAAs can be used as a treatment-as-prevention tool opening the possibility for micro-elimination among subpopulations such as MSM.

Although DAAs have changed the field of HCV, not all patients achieve sustained virological response (SVR). Unfortunately, in real-life data treatment with DAAs fails in approximately 2.5%-5% of patients and this may often occur in the presence of resistance associated substitutions (RAS). RAS exists in different forms. The polymorphisms, which are naturally occurring nucleotide changes, and the RAS that emerge under the pressure of DAA treatment. The frequency of polymorphisms differs between geno- and subtypes, geographical region, and method of sequencing and several elements can influence the emergence of RAS during treatment: viral factors (genotype and fitness of the resistance population); host factors (cirrhosis, previous DAA failure, and IL-28B non-CC; and treatment factors (duration of treatment, adherence, and addition of ribavirin).

Virological failure due to RAS is uncommon. However, owing to the wide distribution and further upscaling of DAAs, it is likely that a significant number of patients will experience virological failure. As an illustration, DAA treatment of 71 million people with HCV could result in approximately 1.8 –3.6 million first-line DAA treatment failures.

There are different reasons why resistance needs addressing in order to reach the elimination goals. First, when virological suppression is not obtained HCV is still transmittable. Furthermore, HCV disease progression will still progress towards development of cirrhosis and a possible hepatocellular carcinoma. Second, resistance will add more steps to the cascade of care, in which optimization is already needed. An RAS leading to resistance requires adequate monitoring and re-treatment after failure, which are two further steps in the cascade of care. This will be a tremendous challenge for certain subgroups, such as people who inject drugs. These subgroups are already difficult to identify and diagnose, let alone follow up for resistance monitoring.
Third, guidelines still contain low-quality and limited real-life data regarding re-treatment strategies. This might lead to treatment failure and patients who are extremely difficult to cure. In addition, resistance testing is performed only in 70% of those individuals whose treatment has failed. Moreover, re-treatment is often not tailored to these results or patients do not receive the recommended second-line treatment. Finally, costs are still a roadblock towards elimination. DAA prices are a restriction in providing full reimbursement. As an example, in some European countries, DAAs are restricted based on fibrosis stage and co-infection status for first line-DAA treatment. Additionally, not all DAA combinations are reimbursed. The most used and reimbursed DAAs are ombitasvir/paritaprevir/ritonavir + dasabuvir (in 94% of the countries) and sofosbuvir/ledipasvir (in 89% of the countries). Sofosbuvir/velpatasvir with ribavirin is only reimbursed in 83% of the countries.

Europe currently accounts for an estimated 3.2 million chronic HCV infections. Approximately 5% (0.4% – 5.6%) of this population is treated and 4% actually cured. In the forthcoming years a further scale-up of DAA use is expected, as more awareness and strategies towards HCV elimination are created to achieve the WHO elimination goals. To reduce the incidence and liver-related mortality, disease progression and transmission must be avoided. Therefore, it is of utmost importance to prevent RAS from emerging and handle the existing polymorphisms adequately.

Additional knowledge based on real-life data is needed in a timely manner. Mutational patterns leading to virological failure need to be identified to tailor first-line DAA treatment. Moreover, additional knowledge is required to identify whether newer antiretroviral regimens are necessary, based on the current mutational patterns leading to virological failure.

Currently, it is difficult to identify these mutational patterns and to provide the necessary information regarding re-treatment. Most European real-life resistance data come from studies with small sample sizes and are scattered among different countries and laboratories. Clinical data often provide the commonly seen genotypes and provide no data on uncommon geno- and subtypes. In addition, available data from clinical trials are selected based on favourable patient characteristics and standardisation methods. Additionally, re-treatment options are becoming scarce, since pharmaceutical companies have stopped the development of newer DAAs.

There are clinical trials that have assessed the efficacy of re-treatment strategies. SVR rates between 86% and 100% were achieved with newer regimens, such as sofosbuvir/velpatasvir combined with ribavirin, sofosbuvir/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir. However, limited real-life data are available on the results of re-treatment options.
In the past, HIV researchers and clinicians have experienced similar obstacles in interpreting resistance data. To address this problem, miscellaneous antiretroviral resistance surveillance databases were established and which have provided data aggregation and have combined with clinical information.\textsuperscript{189,190} Common HIV resistance databases are the Stanford HIV database (HIVDB), EuResist, and SPREAD by the European Society for Translational Antiviral Research (ESAR).\textsuperscript{191,192}

Currently, HEPCARE is the only large international collaboration within Europe combining different national surveillance programs in one central database. HEPCARE is established by ESAR, which has years of experience with HIV resistance surveillance (SPREAD program). The advantage of one central database, compared to separated studies and other cohorts, is that data is no longer fragmented over different centres. The heterogeneity of resistance reporting has made interpretation challenging and has significantly hampered the use of this information in guiding clinical decision-making. HEPCARE provides a standardization of methods that ensures an easier analysis of data and provides insights into circulating resistance patterns as compared to separated cohorts. HEPCARE provides a larger sample size compared to separate study sites and combines data from 18 different European countries and two large national cohorts. It is important to monitor resistance and its spread so that action can be taken when necessary.

HEPCARE will store baseline sequences, enabling a thorough interpretation of viral resistance profiles when treatment fails, as well as identifying previously undescribed RAS associated with treatment failure. By collecting these sequences and storing data, HEPCARE will also become a reference database to compare data between different study sites.

To achieve the WHO 2030 elimination goals, virological failure is an obstacle that needs to be addressed. Virological failure will complicate elimination by requiring different, newer, and longer DAA regimens that may not be readily accessible. Furthermore, it will lead to a group of difficult-to-treat patients who still experience the problems of chronic HCV and who could still transmit the virus.

Tailoring of re-treatment strategies according to resistance profile can prevent multiclass resistance. As with HIV, drug resistance databases provide comprehensive information correlating RAS with clinical outcomes of antiretroviral treatment. A large-scale international collaboration will deliver real-life data needed to provide this essential comprehensive information. HEPCARE is a suitable initiative as a European-framed network, fulfils the need for a larger sample size, a resistance reference database, and an HCV surveillance tool. This initiative, therefore, will significantly contribute to providing the best HCV treatment strategy for patients.
TRANSMISSION OF NS5A RESISTANCE ASSOCIATED SUBSTITUTIONS AMONG MEN-WHO-HAVE-SEX-WITH-MEN RECENTLY INFECTED WITH HEPATITIS C VIRUS GENOTYPE 1A
Abstract

Transmission of direct-acting antiviral (DAA) resistance associated substitutions (RAS) could hamper DAA cure rates and ultimately jeopardize hepatitis C virus (HCV) elimination efforts. A phylogenetic analysis of 87 men-who-have-sex-with-men recently infected with HCV genotype 1a demonstrated that one-third (28/87) belonged to a single large cluster in which 96% harboured the NS5A M28V RAS.
Brief report

In this study we analysed a population of men-who-have-sex-with-men (MSM) diagnosed with a recently acquired Hepatitis C virus (HCV) genotype 1a infection who participated in two trials studying the effectiveness of direct-acting antiviral (DAA) therapy. A recent HCV infection is considered as less than 6 months old using criteria that have been described elsewhere. In both trials patients with a recently acquired HCV infection were enrolled at 11 sites in the Netherlands and Belgium. A total of 44 individuals received boceprevir, pegylated interferon and ribavirin (2013-2014, DAHHS 1 study) while 43 were treated with grazoprevir + elbasvir (2016-2018, DAHHS 2 study). We generated whole genome sequences based on the Illumina sequencing platform from pre-therapy samples in the DAHHS 1 study and HCV NS5A and NS5B genes using Sanger sequencing from the DAHHS 2 (For methods see supplement). The analysis for RAS in the baseline samples showed a very high prevalence of the NS5A M28V RAS, which was present in 31 patients (35.6%, 95% confidence interval C.I. 26.4 – 46.1). This prevalence is substantially higher than the 0-6% prevalence described previously in other studies, including HCV HIV co-infected MSM from Poland.

A phylogenetic analysis showed that 28 of 31 sequences containing a M28V substitution belonged to a single large cluster with a small genetic distance threshold (<3%), representing approximately one-third of all newly diagnosed infections (For methods see supplement) (Figure 1). This high M28V prevalence can be explained by a founder effect (i.e., the occurrence of substitution in high frequency in a particular population). Our M28V cluster could be subdivided into two sub-clusters, one of which contained just the M28V variant whereas in the other sub-cluster in addition to the M28V substitution several other NS5A RAS were observed e.g. NS5A H58P, A62E, and even the Y93H (Figure 1). In 16 of the 28 M28V containing sequences the M28V occurred as a pattern with H58P and A62E. Although these RAS are not considered to be clinically relevant in HCV genotype 1a the high prevalence of the combination supports a founder effect. The M28V RAS was already present in samples obtained in 2013-2014 before the widespread use of DAAs in the Netherlands strongly suggesting that this RAS occurred and spread naturally in HCV1a viruses rather than the result of selective pressure of DAA therapy. We could not identify any association towards RAS pattern and geographic location or patient demographics.

In vitro data shown that the M28V substitution lowers the susceptibility of HCV genotype 1a to the NS5A inhibitors ombitasvir (58-fold change), daclatasvir and pibrentasvir (<2.5-fold change). In addition, there is no indication that the M28V variant decreases the susceptibility of velpatasvir. Furthermore, the M28V substitution was shown to decrease the cure rates of chronic HCV genotype 1a when treated with grazoprevir – elbasvir.
Luckily, the M28V substitution or a combination of RAS including the M28V substitution did not affect the treatment outcome among patients with a recently acquired HCV infection who were treated with a shortened 8-week regimen of grazoprevir + elbasvir. Currently, there are no other reports which discuss the clinical implication of the M28V+H58P+A62E or the M28V+H58P+A62E+Y93H RAS pattern. Nevertheless, the Y93H substitutions as a singleton confers high (>100 fold-change) resistance to NS5A inhibitors as daclatasvir, elbasvir, ledipasvir, and velpatasvir and low (<10 fold-change) resistance to pibrentasvir in vitro.

The transmission of RAS carrying viruses has been described previously, although the transmission of an NS5A RAS in such a large cluster has not been reported before. Transmission of the M28V RAS was previously described among five MSM in France. Additionally, the NS3 RAS V36M and in particular the Q80K was reported to be more prevalent among HCV HIV co-infected MSM, of which the Q80K occurred in several clusters. The presence of the Q80K had large clinical implications since the susceptibility to simeprevir lowered in genotype 1a patients. Therefore, clinicians were advised to analyse the presence of Q80K prior to simeprevir treatment among genotype 1a infected patients. Although pibrentasvir and velpatasvir containing DAA regimens are highly effective also against viruses with RAS, caution remains required. Firstly, the availability of these DAA regimens may differ geographically. Secondly, outbreaks of HCV infections and transmission to sex or needle-sharing partners continue to occur. Our observation illustrates that transmission of DAA-resistant variants can continue to occur over a prolonged period. This may be partly explained by the persistence of NS5A inhibitor resistant viruses in patients.

Currently, only 5 million of the total 71 million HCV-infected individuals have been treated. The spread of RAS containing viruses may, in case they affect local cure rates, jeopardize global HCV elimination efforts. With a further roll out of DAA therapy on a global scale surveillance for the spread of RAS is recommended. In case of significant transmission rates of clinically relevant RAS-containing viruses targeted precautions can then be taken.
Figure 1. Phylogenetic analysis of a concatenated NS5A and NS5B alignment showed a cluster including 28 MSM (HIV-infected (n=27) and HIV-uninfected (n=1). 96% of individuals in this cluster harboured an NS5A M28V containing variant. All patients in this cluster treated with an NS5A-inhibitor (GZR/ELB for 8 weeks) obtained a sustained virological response. The sequences depicted with green are collected prior to the massive DAA therapy uptake in 2015, the sequences depicted with blue in the years thereafter. The cluster had a bootstrap value and Shimodaira Hasegawa like approximate likelihood ratio >90 and a genetic distance <3%. (for methods see supplement).
Supplement

Study population
A detailed description of the studies and patient inclusion criteria can be found elsewhere\textsuperscript{74,132}. In summary, both DAHHS studies enrolled participants identified with an acute HCV infection during routine clinical care in ten different Dutch HIV treatment centers. Additionally, during the DAHHS 2 study, one Belgian HIV treatment center (Antwerp) participated and patients from all over Belgium were referred to this center for participation in the study. In both studies, patients were included if HCV had been diagnosed within six months after HCV infection as described elsewhere\textsuperscript{74,132}. All patients gave written informed consent for the use of their blood samples for research purposes\textsuperscript{74,132}.

Sequencing
Different methods for sequencing were used in the two DAHHS studies\textsuperscript{74,132} respectively next-generation sequencing (NGS) in DAHHS 1 and Sanger population sequencing in DAHHS 2. In short, DAHHS 1 samples were sequenced by NGS on the Illumina MiSeq platform as previously published\textsuperscript{151}. The CLC Genomics Workbench (version 7.5/7.5.1) including the CLC Microbial Genome Finishing Module (version 1.4, Qiagen) was used to process the raw reads into full-genome consensus sequences. Trimmed reads were prefiltered against a GenBank reference list containing 953 partial and complete HCV genomes, followed by the sampling of a subset of 50,000 to 100,000 HCV-specific sequence reads for \textit{de novo} assembly of whole genomes\textsuperscript{151}. For subsequent phylogenetic and resistance analysis only the nucleotide sequences of the NS5A and NS5B region were used. For DAHHS 2 samples the NS5A and NS5B genes were amplified by PCR and subsequently sequenced by Sanger sequencing as described before\textsuperscript{132}.

Resistance analysis
For our resistance analysis we used baseline sequences, defined as the sequence from the sample before start of therapy. All baseline sequences were aligned and trimmed to equal length with the genotype 1a reference strain H77 (AF011753) using Muscle. Clinically relevant RAS were defined as amino-acid changes as compared to H77 at positions 24, 28, 29, 30, 31, 32, 38, 58, 62, and 92 for NS5A and 159, 282, 316, 320, and 321 for NS5B, as described in the EASL guidelines\textsuperscript{205}. We used a >15% cut-off for variant calling for the sequences generated using NGS\textsuperscript{194}. 95% confidence intervals (CI) were calculated with the Wilson score interval. Proportions were statistically compared using a chi-square test.
Phylogenetic analysis
A concatenated alignment of 87 NS5A and NS5B sequences was assembled. For each of these HCV sequences the 80 most highly similar HCV sequences were selected as control sequences from GenBank using BLAST (Basic Local Alignment Search Tool). After removal of duplicate sequences, phylogenetic analysis was based on 87 study samples and 425 publicly available control sequences. We included a genotype 1b sequence (EU482849) to root the phylogenetic tree. A maximum likelihood analysis was performed using a generalized time-reversible model (GTR) with a 4-category discrete gamma rate model while accounting for invariable sites using the IQTree software. Tree robustness was evaluated using 1000 ultra-fast bootstrap replicates and a Shimodaira-Hasegawa-like (SH-like) approximate likelihood ratio test. A cluster was defined based on a minimum ultra-fast bootstrap support of 90%, an SH-like approximate likelihood ratio of at least 80%, and a genetic distance threshold of 3%. The genetic distance was calculated using a Tamura and Nei model with a 4-category discrete gamma distribution with the software MEGA 10. A transmission pair is defined as two sequences clustering together.
Part 3
DISCUSSION
General discussion and future perspectives

Discussion

The firm recommendation of the WHO and UNAIDS to eliminate HCV and HIV as a public health threat by 2030 requires a deeper investigation of several topics. The central aim of this thesis is to discuss the elimination of disease and the burden of disease in the context of a curable disease (HCV) and chronic infection (HIV). Both viral diseases have an enormous public health impact. Moreover, they require expensive or lifelong antiviral therapy which leads to exorbitant healthcare costs. Therefore, this thesis aims to offer elimination strategies and further insights which can reduce cost and/or increase health benefit. In the following paragraphs I will discuss my recommendations based on our research and propose future perspectives.

Immediate direct-acting antiviral agents for all HCV-infected patients

The high cost of direct-acting antiviral agents (DAAs) was a major challenge towards therapy availability. Therefore, DAA therapy was prioritized based on liver fibrosis stage (F2/F3 METAVIR score) and further restricted based on the prescribing specialist and recent substance abuse (e.g., alcohol or drugs). Cost-effectiveness studies showing the financial and public health benefit of early treatment could help to lift restrictions on treatment to these categories of patients.

The Netherlands was the first country in which DAA therapy became unrestrictedly available halving HCV incidence among HIV-infected MSM in the year thereafter. Chapter 2 was the first study which showed cost reduction and substantial health benefits by treating recently acquired HCV infections. Chapter 2 also showed that delaying DAA therapy resulted in an increase of HCV incidence, prevalence, and the number of hepatocellular carcinomas.

By 2017, several European countries still had reimbursement restrictions. Data supporting immediate DAA treatment combined with strong leadership and governance (by government, policy-makers and treating physicians) has lowered list prices and more advocacy from community-based organizations have helped to lift reimbursement restrictions in Europe. Unfortunately, some countries, such as Thailand where HCV is emerging among HIV-infected MSM, still restrict DAA treatment until F2 fibrosis stage. The model from Chapter 2 calibrated to Thai epidemiological data was used to show that DAA treatment is cost-saving in Thailand. I am convinced more of these initiatives and collaborations are needed to increase the advocacy for immediate treatment so that all patients across the world can have access to curative medication which will in turn reduce the global health burden of HCV. Public education can build awareness of the burden of disease and association with liver cancer increasing advocacy by civil societies to call on political leaders to commit national resources to HCV elimination.
Nevertheless, cost-effectiveness outcomes as compared to a cost-effectiveness threshold are hotly debated and the willingness-to-pay threshold (WTP) used to determine a cost-effectiveness threshold varies greatly across continents, countries, and even within countries themselves.\(^{269-271}\) When looking at disease eradication, however, the WTP of a given country may exceed the generally accepted WTP.\(^ {271,272}\) In the case of HCV, we may be looking at the end of the “U-shaped” curve observed in health economics- the cost to reaching the first few patients is very high, then there are economies of scale, and then costs start to increase again when there are just a few remaining cases.\(^ {273}\) Given that DAAs will play a strong role in disease elimination, a higher WTP may be considered, and/or patients and physicians should advocate for more reasonable pricing.

### Population specific HCV monitoring and screening

To provide immediate DAA therapy, recently acquired infections among HIV-infected MSM must be diagnosed in a timely manner. HCV can be diagnosed by several methods, however not all are suitable to detect recently acquired HCV infections. Among HIV-infected MSM, HCV is currently monitored through annual HCV-antibody tests and bi-annual ALT measurements.\(^ {57}\) An elevated ALT is followed-up by an HCV-antibody test, and if HCV-antibodies are present followed-up by an HCV-PCR test. This testing approach may, however, not identify new infections in a timely manner as ALT levels may fluctuate over time and the HCV-antibody response can be delayed.\(^ {84}\) There is therefore a need to evaluate different HCV monitoring strategies including different diagnostic tools.

To address the need of identifying new HCV diagnosis in a timelier manner, Chapter 3 presented the cost-effectiveness of different HCV monitoring strategies among HIV-infected MSM followed by immediate DAA therapy. In Chapter 3 I showed that screening for HCV using the HCV-core antigen (HCV-cAg) which has a comparable sensitivity as the HCV-PCR but which is less costly, reduces the HCV incidence in a high-risk population and reduces costs as compared to a HCV-PCR test.\(^ {11,274}\) Therefore, the HCV-cAg is highly suitable in daily care.

Current guidelines recommend monitoring patients engaged in activities with an increased risk to acquire HCV every three to six months.\(^ {57}\) In my opinion the identification of patients with ongoing HCV risk factors is challenging. Patients may not always disclose risk behaviour, such as IDU, chemsex or MSM due to the feelings of stigmatization and criminalization.\(^ {142,143}\) Therefore, we defined our high-risk group in Chapter 3 as people who were previously HCV infected. Reinfection rates in MSM populations are high and of those previously HCV infected, a quarter to one-third is reinfected within two years.\(^ {71,84,131}\) This population is, thus, highly suitable for targeted monitoring strategies. Another method to identify high-risk behaviour is to implement
targeted monitoring strategies by using a self-reported risk-score. A risk assessment tool is highly suitable in places where MSM are not regularly monitored for HCV, such as the general practitioner’s office or sexual health clinic.

As a part of the MSM community continuously engage in high-risk behaviour I advocate for a highly sensitive one-step diagnostic tool. A one-step diagnostic tool would reduce the time to diagnosis and consequently towards therapy. This test is preferably a self-test which removes the experience of stigma or the barrier to ask their physician “again” for an HCV test. Moreover, self-tests can be available at location where high-risk practices are performed, such as gay saunas and sex clubs or easily ordered online. Several initiatives are currently evaluating the effect of HCV self-testing in the Netherlands. A more creative and ‘out of the box’ way of testing is imperative in this population to reduce onwards HCV transmission. The affected community should be involved to determine which methods fit their needs.

Case-finding for HCV is still a major challenge in many countries as only an estimated 13 million people are aware of their HCV infection. Therefore, the WHO recommended focussed testing in the most affected populations (such as, PWID, baby boomers, people in prisons, MSM, sex workers, and HIV-infected), as well as those with a clinical suspicion of chronic viral hepatitis. Among people who inject drugs (PWID) I would recommend HCV screening with a one-step approach similar as among MSM followed by immediate DAA therapy (Table 1). This is required to avoid losing people out of care. Furthermore, these services should be integrated in HIV-care, needle and syringe programs, or opioid substitution therapy. For the baby boomer population in the United States and Canada, I would suggest a different approach, as this population often does not engage in high risk behaviour. For this group HCV-antibody tests are highly suitable as they detect chronic HCV infections and are not costly. Importantly, as many people require screening a similar structure as the COVID-19 drive throughs would be highly suitable. Among sex workers and people living with HIV I would use a risk score or previous HCV infection to determine if they require a one-step highly sensitive test (Chapter 3) similar as high-risk MSM. Also for this population self-test would be a great option as it lowers the barrier to testing. People in prison can be screened with HCV-antibodies when arriving in prison. If followed by immediate DAA therapy, annual HCV monitoring with an HCV-antibody test is then sufficient. If ongoing HCV transmission takes place, I would recommend using the HCV-cAg as this test is highly sensitive in detecting recently acquired HCV infection and cheaper compared to the HCV-PCR. The cost of treatment often challenges correctional institutions to start HCV screening and treatment. Nevertheless, there is a great public health benefit when HCV-infected individuals are treated in prisons as untreated HCV infections eventually result in cirrhosis and subsequently additional cost. Therefore, political support should be increased.
Table 1. Recommended population specific HCV monitoring and screening

<table>
<thead>
<tr>
<th>Population group</th>
<th>Recommended HCV monitoring or screening approach</th>
</tr>
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<tr>
<td>HIV-infected MSM</td>
<td>One-step diagnostic tool (HCV-cAg or Self-test) targeted to high-risk sub-population (previously HCV infected or through risk-assessment). (^{275,276,278}), Chapter 3. Self-tests available at locations where high-risk practices take place.</td>
</tr>
<tr>
<td>People who inject drugs</td>
<td>One-step diagnostic tool followed by same day DAA treatment. Services should be integrated in needle and syringe programs, or opioid substitution therapy. (^{280,281})</td>
</tr>
<tr>
<td>Baby boomer population (USA and Canada)</td>
<td>HCV-antibody testing. Screening can be integrated in the drive-through testing locations for COVID-19 as these are equipped to test many in a short amount of time.</td>
</tr>
<tr>
<td>Prisoners</td>
<td>Prisoners should be screened with HCV-antibodies upon arrival. Annual HCV monitoring for all prisoners with HCV-antibody test to identify ongoing transmission. The HCV-cAg can be used as confirmation as the costs are lower than the HCV-PCR. (^{11,274})</td>
</tr>
<tr>
<td>Sex workers</td>
<td>Similar approach as to HIV-infected MSM</td>
</tr>
<tr>
<td>Resource limited settings</td>
<td>One-step diagnostic tools such as the HCV-cAg (Chapter 3) or in more rural areas a point-of-care-test. (^{11,274,280,284}) Screening and care should be integrated. (^{16,20,285})</td>
</tr>
</tbody>
</table>

In resource limited settings screenings programs often lack coverage due to the high cost of HCV diagnostics. \(^{285}\) In these settings, cheaper one-step diagnostic tools such as the HCV-cAg (Chapter 3) or in more rural areas a point-of-care-test, which requires less equipment can be recommended. \(^{11,274,283,284}\) Especially in rural area, where people often have to travel far for hospital visits, a one-step diagnostic tool can help to avoid losing people out of the care cascade. Importantly, HCV screening can be integrated in the already existing HIV-care to reduce cost. Other options to increase the financial feasibility of elimination programs are by reducing the cost price of the diagnostic tool used. Egypt for example, a resource limited country that had millions to test and treat, negotiated massive purchasing prices reducing the HCV-PCR price. \(^{285}\) Additionally, the development of novel cheaper point-of-care tests and other HCV diagnostics should be encouraged. Furthermore, data on the effectiveness of various testing programs among key populations in resource limited settings should be investigated. This all should be combined with governmental support and the advocacy of several stakeholders to result in sustainable HCV elimination plans.

Real-time phylogenetic surveillance

Although the elimination strategies outlined in Chapter 2 and 3 reduced HCV incidence among HIV-infected MSM, elimination was not achieved. More insight into the HCV transmission among HIV-infected MSM can help to determine additional elimination strategies.
We used phylogenetic analyses to increase insight into the transmission of recently acquired HCV infections among MSM. Chapter 4 identified several large clusters of recently acquired HCV infections. Clusters contained HCV infections from the period before and after unrestricted DAA use in 2015. Interestingly, over time cluster size remained stable and HCV transmission remained present in several clusters.

These findings outline sub-populations with ongoing transmission where targeted monitoring strategies as discussed in Chapter 3 could be implemented followed by harm reduction programs. Moreover, this epidemic is highly suitable for contact tracing and (anonymous) partner notification. After implementation a follow-up, ideally with real-life phylogenetic analysis, tracking the effect of the implemented monitoring strategies should be considered. Next gene sequencing (NGS) is favourable over a short NS5B segment as a higher phylogenetic signal can be obtained. This provides more information regarding the spread of HCV, especially when transmission events occur in temporal proximity. Combined with demographical data, a real-life phylogenetic surveillance would provide an excellent addition to the existing elimination strategies. Nowadays, during the COVID-19 pandemic real-life phylogenetic analysis can play a major role indicating transmission hotspots. Insight into the SARS-CoV-2 transmission dynamics can inform policy makers in more details so that regional measurements as increased testing, local lockdowns, or prioritize regions for vaccination. Ideally, HCV real-life phylogenetic surveillances take place on an international level as HCV is not restricted by borders. The established HCV resistance surveillance (Chapter 5) could be used as sequences are already being collected.

Chapter 4 only included patients with recently acquired HCV infections. Prior to the high DAA up-take there were many chronically HCV-infected patients in the Netherlands. Although most chronically HCV-infected patients are cured the interaction of recently acquired with chronic HCV infections is still valuable information for elimination strategies. If the HCV epidemic among MSM is fuelled by an unidentified or uncured chronically HCV-infected population, there should be more focus towards HCV-case finding. Therefore, I would recommend analysing this interaction through phylogenetic analysis. Moreover, new phylogenetic analysis should consider the influence of HCV from neighbouring countries. In some countries reimbursement restrictions were longer present, which could have negatively influenced the effect of unrestricted DAAs in the Netherlands. Koopsen et al. recently showed several new HCV introductions in the MSM population of Amsterdam. This trans-national importation of HCV could hamper elimination efforts in the Netherlands, therefore a broader European approach towards HCV elimination is advised. The networks identified in Chapter 4 could therefore be part of a large European network of HCV infections. This hypothesis is
further supported by the M28V harbouring variant detected in French and Dutch MSM populations as discussed in Chapter 6. The limitation of the spread of HCV through travel, requires a more European approach towards HCV elimination.

In resource limited settings, HCV sequencing and especially NGS might not be feasible due to shortage in resources. Currently, establishing surveillance tools for epidemic preparedness programs is already a difficult task in resource limiting settings. A cross-sectional surveillance would be a first option, as current focus is on establishing effective screenings and treatment programs. The surveillance can be than be repeated after a few years.

Ongoing HCV resistance surveillance

The highly effective DAAs play a major part in HCV elimination. Unfortunately, in rare cases patients fail DAA treatment, often in the presence of resistance associated substitutions (RAS). As 71 million people still require treatment, this could eventually lead to a substantial number of first line DAA failures. Especially, in resource limited settings where regimens are often older (more prone to resistance) and limited by the number of DAA compounds. RAS may jeopardize the elimination goals resulting in continuous transmission and disease progression will continue.

In Chapter 5 a resistance surveillance was proposed, collecting sequences at baseline prior to- and after failure of DAA therapy. Data from the HepCare cohort (Chapter 5) showed several clinically relevant NS5A RAS at baseline and a high number of RAS after failure. Compared to baseline data from HepCare we identified a high prevalence of the NS5A M28V RAS in our MSM cohort in the Netherlands. Chapter 6 showed rapid spread of the M28V variant among a population with ongoing HCV transmission. Moreover, the DAA-resistant variant remained present over a prolonged period. Resistance surveillances are not only key for HCV, but also important for other viral diseases. Good surveillance systems can timely detect the spread of new circulating variants, such as the new SARS-CoV-2 mutations currently emerging in the United Kingdom and South-Africa.

The findings from Chapter 5 and Chapter 6 have several implications. First, the spread of RAS, which lower cure rates, can jeopardize elimination efforts. The reported M28V RAS did not affect cure rates as no reduction in susceptibility to the DAA regimens used in our population was seen. Nevertheless, other variants may spread which do influence the susceptibility to certain DAA regimens. Second, although newer DAAs have even higher curates there are rare occasions when treatment still fails. Third, Chapter 6 showed the persistence of the M28V RAS over time. Importantly, the M28V containing cluster present in Chapter 6 also included other NS5A RAS emphasizing the
possibility of accumulation of RAS. Multiple RAS are also found in various “unusual subtypes”, defined as genotype (GT) non 1a/b, GT2 non 2a/b, GT3 non 3a, GT4 non 4a/d, and GT6 which are common in regions where few clinical trials have been performed. For instance, the “unusual subtypes” represent an estimated 5.5 million HCV infections localized in Sub-Saharan Africa (SSA) and almost 10% of infections in South-East Asia. “Unusual” subtypes, however, have been associated with lower response rates due to various polymorphisms at relevant amino acid positions. More insight into these polymorphisms and their effect on the DAAs can be obtained by aggregating data. The knowledge obtained can further guide treatment programs, especially in resource limited settings, where “unusual subtypes” are mostly common. Therefore, these data advocate the need for an ongoing resistance surveillance, focusing on “unusual subtypes”. Importantly, the surveillance can be combined with real-life phylogenetics as discussed in the previous chapter.

Improving the general practitioners’ guidelines for earlier HIV case finding
The UNAIDS 90/90/90 goals for HIV elimination have been achieved in the Netherlands. Nevertheless, half of PLWH present late to care comparable with other European countries. Late presentation is associated with a high morbidity, mortality, and continuously spread of HIV. Programs identifying patients earlier will, therefore, have a substantial benefit.

It is important to identify patient populations with a high risk for late presentation and determine the direct medical cost. The additional cost of late presentation can be allocated to strategies focused on earlier HIV-case finding. Therefore, Chapter 7 analyzed the cost of HIV-care based on time of presentation over a five-year period after ART initiation. Chapter 7 showed considerable higher short-term HIV-care cost among late presenters (CD4 200-350) and more specifically very late presenters (CD4 <200). These higher cost per patient persisted at five years post ART initiation driven by non-ART cost (inpatient days, co-medication, and outpatient appointments).

In order to develop strategies to find late presenters, insight and understanding of these populations is required. Chapter 7 showed mostly non-Western migrants, heterosexuals, and elderly people present during a late stage of infection. Compared to MSM, who are more often aware of the risk to acquire HIV, these patient groups are frequently unaware of their risk. Therefore, it is unlikely to detect these infections in a sexual health clinic while a great role can be played by the general practitioner (GP) who is more frequently visited in the years prior to an HIV-diagnosis.
The needed improvements that would increase the possibility for earlier HIV case finding at the GP are the following. First, the GP-guidelines (NHG) should have an HIV-specific standard. In the current guidelines HIV is embedded in the sexually transmitted infection (STI)-standard. Additionally, there is an in-depth document regarding HIV which is not in the actual NHG guidelines. Many GPs are only familiar with the NHG-standards and not the attached and even, if a GP is searching for an indicator disease in the NHG there is no link to this in-depth HIV-document. Importantly, AIDS-defining illnesses also are not discussed or mentioned in the STI-standard and therefore the link with HIV cannot be made. The lack of public knowledge of HIV and their asymptomatic nature, many patients with STI or HIV and many do not classify themselves as at risk for an STI, leading to GPs perhaps not consider testing for HIV. Therefore, HIV should have its own standard in the NHG guidelines. Second, the STI-standard recommends HIV-testing among people from STI-endemic countries. However, most of the GPs probably do not know STI-endemic countries by heart. Hence, the new HIV-standard or the STI-standard should have a list with STI-endemic countries and the prevalence of different STIs (HIV, HBV, HCV). Additionally, these population groups should be regularly monitored for HIV and HBV which can be performed when blood is drawn or at least every other year. Lastly, GPs should be advised to document the sexual orientation or ethnic background from patients. Callander et al. showed that sexual orientation recording was higher in clinics with a high caseload of gay/bisexual patients. This could emphasize unawareness of the importance of the topic or neglecting the topic. Therefore, opting for a standardized question on sexual preference at a first consultation could be a step towards a solution.

In African countries more patients present late to care than in European countries. Currently, there are no studies assessing the additional cost of presenting late in African countries. Factors related to late presentation on the African continent included stigma, low monthly income, lack of HIV related information, but also geographic region and psychosocial factors. Strategies as discussed above might not be suitable for this population and more research is needed to identify which interventions work best and where.

**Quality of life measurements in standard of care**

Quality of life (QoL) is important in HIV-care, due to the chronic nature of the disease, and should therefore be regularly monitored. Moreover, QoL in the form of a utility score is an important factor in cost-effectiveness analysis.
QoL consists and can be influenced by several aspects of life and is defined as the individual’s perception of physical and mental health over time. In Chapter 8 we compared the QoL of PLWH in two European countries with their general population. Generally, the results of Chapter 8 showed a comparable QoL among PLWH from the Netherlands and England with the general population. However, PLWH reported twice the amount of anxiety and depression symptoms than the general population. Chapter 8 showed that ART is very successful in helping to reduce inequalities in QoL. This further highlights the importance of earlier HIV-case finding. The gains in QoL and decrease of extra cost of earlier presenters as outlined in Chapter 7 could be substantial when scaled up to more countries.

Several factors could contribute to an increase in anxiety/depression among PLWH, reported in Chapter 8, such factors are, for example, coping with a recent HIV diagnosis, the onward effect on relationships, stigmatization, social isolation and loneliness, and the experience of living with a chronic illness. More attention towards reducing mental health issues are key to reducing transmission as (untreated) mental health issues are associated with non-adherence and increased high-risk behaviour. Lack of good mental health may facilitate HIV transmission, which can hamper the other ‘90-90-90 targets’. A standardized QoL measurement in HIV-care can identify patients with mental health issues. A more in-depth screening with a questionnaire that can identify depression, such as the HADDS should then be the second step. If an anxiety disorder or depression is present, a multidisciplinary team should be involved. Currently, PLWH are often referred to another centre specialized in mental health issues and recommendation would be that these specialists are integrated in the HIV-treating facility and part of standard HIV-care.

Lazarus et al. proposed that progressing towards the UNAIDS elimination targets QoL should be adopted as a ‘fourth 90’. I agree with this as obtaining the ‘fourth 90’ is important to ensure that long and healthy lives are possible for PLWH. Hence, QoL measurements should be adopted as part of regular HIV-care. However, there is no consensus towards the best instrument among PLWH. Chapter 8 used the EQ-5D-5L questionnaire. While the EQ-5D-5L may be less sensitive to HIV-specific changes than other instruments, it is useful due to its extensive validation, brevity, ease of administration and interpretation, the availability of several languages, and allows comparison to the general population. Other topics as sexual health, stigma, social support, and mental health are not incorporated in the EQ-5D-5L. Other instruments, such as the WHOQOL-HIV or MOS-HIV or other patient-reported outcomes (PROs) could be used to determine issues on these domains. Most importantly, the affected community should be involved in determining the essential aspects of the ‘fourth 90’.
Future perspectives

Integration and decentralization of care
For both HCV and HIV monitoring and testing programs should be integrated in existing prevention, care, and treatment services. In that way the functionality of the existing facilities is maximized which in turn reduces costs. Moreover, decentralization of care is an opportunity to reach populations unaware of their acquired infection as the accessibility to the facility and barrier towards testing might be lower.

Many patients infected with HCV many patients are still unidentified. Integrated HCV screening can help to reduce cost and combine efforts. In Georgia, for example, HCV screening is integrated with HIV and TB screening. Additionally, Georgia uses a decentralized approach which helped to make substantial progress towards eliminating HCV with over 50% of persons with chronic HCV infection diagnosed, most of whom have initiated treatment and high cure rates are being achieved. Integrated and decentralized HCV treatment has been successful and improved linkage to care.314 Also HCV, or eventually HIV, treatment can be decentralized to primary care among patients with low fibrosis grades (<F2). Australia redefined linkage to care models where patients were more likely to engage in care when HCV-care was decentralized and provided in primary care compared to tertiary hospitals.315,316

There are several examples of integrated care, such as antenatal HIV and hepatitis B screening, combined HIV/HCV and HBV screening in tuberculosis entry screening, and combined HCV+HIV screening.317-319 Although several HIV-screenings programs are available in the Netherlands PLWH presenting late in HIV-care still are a challenging population. Apparently, these patient populations do not engage in already present screenings programs and therefore a different approach is needed.227 HIV screening programs could be performed at the GP and combined with other diseases such as diabetes.16 Cost-effectiveness studies can help to determine in which areas these screening programs would be cost-effective based on the patient population.320

Part of the current COVID-19 testing locations showed the feasibility of large-scale testing on location. This option should be explored for integrated testing of other viral diseases such as HIV, HCV, and HBV combined with screening for other diseases such as, diabetes, hypertension, or vaccination programms.16,285 Integration of screenings programs will save cost as direct labour and overhead expenses will reduce. Moreover, decentralizing care, by for example using a mobile test van can reach areas where people live who have trouble accessing health-care services.321
The use of artificial intelligence and E-health

In the upcoming years, the role for artificial intelligence (AI) and E-health in the elimination of disease and the burden of disease is likely to increase.\(^{322}\) AI involves several techniques including machine learning, neurolinguistic programming and deep learning. E-health is referring to health services and information delivered and enhanced through the internet and related technologies, such as apps.\(^{323}\)

For the field of HIV there are already several programs which provide E-health solutions as for example, the Happi-app an app in which a patient can answer questions regarding their health and access information regarding medication and laboratory measurements.\(^{324}\) QoL questionnaires as discussed in Chapter 8 can easily be monitored in an app or other digital platform. Moreover, outpatient visits can be replaced by a short e-consult if a patient feels well and QoL is good. This might also reduce stigma as outpatient visits are less needed and it is easier to raise difficult issues in the comfort of your own home. On the contrary, as other PLWH are often overwhelmed by the social and psychological aspects of disease. In such a situation, a short chat on a platform with anonymous other PLWH or an online chat with a specialized nurse may ease the mind. Nevertheless, a balance between E-health and personal contact is important for optimal personalized care and should be subjected to further studies also considering cost-effectiveness. Furthermore, E-health apps could measure the symptoms and determine when an extra consultation is needed. The goal in moving forward is to a more patient centred care E-health, possibly combined with AI algorithms can determine who needs additional care.

One of the opportunities from E-health, is the facilitation of remote care and home delivery. Especially, for elderly PLWH traveling to the hospital might be challenging.\(^{325}\) Although E-health can be a great solution for some people, it is not feasible for others. There are still patients which cannot read or do not have access to a smartphone. Unfortunately, this population is often the population which Chapter 7 defined to be late in care.

Apps which are not established as an E-health app, such as Grindr (sexual dating app) can link high-risk individuals to self-testing platforms.\(^{326}\) This can be a useful addition to elimination strategies outlined in Chapter 2 and 3. Moreover, it can saves on total societal costs as patients are diagnosed earlier and testing is targeted to a high-risk population. Also, during the current COVID-19 pandemic apps are shown to be useful as they provide a warning signal after being close to an infected person for 15 min. This type of location based can be used among other infections with ongoing transmission.
Another method to track people at risk for infections is through AI. AI can help to identify patients at risk to acquire or with HCV or HIV based on medical records and patient data. Several initiatives are using AI to select potential candidates for HIV preexposure prophylaxis based on the indicative text of high-risk behaviour, and to efficiently guide risk-adapted HCV screening in a population with low incidence.\textsuperscript{327-330} Therefore, AI algorithms are highly suitable in identifying late presenters (Chapter 7), populations who require targeted monitoring (Chapter 3 and 4), but also to track and diagnose other viral infections. Ethical concerns regarding the guarantee of privacy and securing data are however still an issue. I foresee a great role for AI and E-health in eliminating disease and the burden of disease.

Conclusion

This thesis showed that elimination of HCV and burden of disease of HIV infection requires an integrated and targeted approach. In my opinion there are a few recommendations which needs addressing in terms of the WHO and UNAIDS elimination goals. First, immediate DAA treatment should become available for all HCV-infected patients. Second, monitoring and screening strategies should be population specific based on epidemiology, risk behaviour and available resources. Third, surveillances tracking the spread of new infections and resistance should be in place guiding monitoring strategies and informing on DAA therapy regimens. Moreover, surveillances are important in terms of epidemic preparedness. Fourth, GP guidelines for HIV can be improved to optimize earlier HIV-case finding. Moreover, AI algorithms can identify risk factors or undiagnosed HIV infections from medical files. Fifth, integration and decentralization of care can reduce cost and maximize efficiency. Furthermore, it increases accessibility and lowers barriers for care. Lastly, ensuring a good QoL is key in elimination of the burden of disease. Therefore, QoL should be adopted as standardized measurement in care and as the ‘fourth 90’ of the UNAIDS goals. E-health is the next step in health care supporting current practices and the first step towards more personalised HIV-care.
NEDERLANDSE
SAMENVATTING
Hepatitis C

Natuurlijke beloop
Hepatitis C is een virale infectie die een ontstekingsreactie aan de lever veroorzaakt, oftewel hepatitis. Wanneer iemand geïnfecteerd raakt met het hepatitis C virus (HCV) kan het lichaam in 15-20% van de gevallen het lichaam opruimen, of wel klaren. Als HCV niet geklaard wordt ontstaat er een chronische hepatitis. Bij een chronische hepatitis sterven de levercellen af en ontstaat er verlittekening, genaamd fibrose. Er zijn vier verschillende stadia van fibrose waarbij stadium 4 (cirrhose) het ergst is. Over een verloop van tientallen jaren resulteert een onbehandelde HCV infectie bij een aantal patiënten in fibrose en uiteindelijk cirrhose. Een cirrhotische lever is erg star en geeft veel tegendruk aan het bloed waardoor er vocht in de buikholte ontstaat of spataderen in de slokdarm. Verder vermindert de normale leverfunctie wat klachten geeft als stollingsstoornissen, jeuk, vermoeidheid, geelzucht of verminderde eetlust. Deze symptomen kunnen worden behandeld of ondersteund. Herstel van de leverfunctie is echter alleen mogelijk door de oorzaak, HCV, weg te halen. Zonder HCV behandeling kan iemand uiteindelijk sterven aan zijn leverziekte. Daarnaast is er vanaf fibrose stadium 3 is er een verhoogde kans op een hepatocellulair carcinoom. Een hepatocellulair carcinoom heeft een slechte prognose waarbij ongeveer 80% van de mensen binnen vijf jaar is overleden.

Voorkomen en verspreiding
Wereldwijd zijn er ongeveer 71 miljoen mensen geïnfecteerd met HCV. Per land zijn er grote verschillen in het aantal HCV geïnfecteerde mensen. Het verschil in aantallen (prevalentie) heeft voornamelijk te maken met de verschillende verspreidingsroutes van HCV. Egypte, bijvoorbeeld, had de hoogste HCV prevalentie van de wereld. Veel mensen kregen HCV doordat er tijdens een vaccinatie programma slecht gedesinfecteerde naalden werden herbruikt. In deze setting verliep de HCV verspreiding dus via besmette naalden. Dit is tevens het geval bij drugs gebruikers of prikaccidenten in het ziekenhuis. In veel landen werden tot voor kort de bloedproducten niet op HCV gecontroleerd en werden mensen besmet door een transfusie.

In Nederland komt HCV vooral voor onder HIV-geïnfecteerde mannen die seks hebben met mannen (MSM). Sinds 2000 was er een stijgende lijn in het aantal HCV infecties onder HIV-geïnfecteerde MSM gerelateerd aan seksuele transmissie, maar was HCV overdracht onder heteroseksuele koppels zeldzaam. Voortschrijdend inzicht toonde aan dat sub-groepen binnen HIV-geïnfecteerde MSM extreem hoog risicogedrag vertoonden, namelijk onveilige seks met verscheidende partners, gedeelde seksspeeltjes en drugs gebruik tijdens seks (chemsex). Kenmerkend voor deze populatie is het veelvuldig voorkomen van re-infecties door voortdurend risicogedrag. Behoudens Nederland komt HCV onder HIV-geïnfecteerde MSM ook veel voor in andere westere Europese landen denk aan Engeland, Duitsland, Belgie en Frankrijk.

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Diagnostiek en de behandeling

Er zijn verschillende methodes om HCV te diagnosticeren. De meest gevoelige methode is de HCV-PCR. De HCV-PCR detecteert al snel, 10-14 dagen, na besmetting HCV virus deeltjes in het bloed. De HCV-PCR is alleen een vrij dure techniek (€120 - €220) en wordt daarom niet gelijk ingezet. HCV-antilichamen kunnen ook worden gedetecteerd maar pas na weken tot maanden na de besmetting. Bij HIV-geïnfecteerde mensen kan dit echter nog langer duren. Na het spontaan verder verdwijnen of behandelen van HCV blijven HCV-antilichamen detecteerbaar. Ook kan ALAT (enzym verhoogd bij hepatitis) gemeten worden, maar ALAT kan flucturen over tijd waardoor een HCV infectie kan worden gemist. Daarnaast is ALAT niet specifiek voor HCV en kan het ook door andere redenen verhogen. Het meten van ALAT en HCV-antilichamen is wel veel goedkoper dan de PCR.

De behandeling van HCV was tot een aantal jaren geleden met 48-72 weken peginterferon alfa (PEG-IFN). PEG-IFN geeft vervelende bijwerkingen bij >10% van de mensen zoals hoofdpijn, misselijkheid, buikpijn, depressie, angsten, slapeloosheid en vermoeidheid. De behandeling werd daarom door veel mensen geweigerd. Verder was de effectiviteit van PEG-IFN minder dan 50%.

Gelukkig is er sinds 2014 hoop voor mensen geïnfecteerd met HCV. Er kwamen nieuwe revolutionaire medicijnen op de markt, direct werkende antivirale middelen (DAAs). DAAs hebben een hoge effectiviteit, 90-95% genezing, en een laag bijwerkingen profiel. Een 12 weken durende kuur is echter zeer prijzig, namelijk €40.000. Vanwege deze hoge prijs werd er besloten om de behandeling met name aan te bieden aan patiënten met ernstige fibrose. Daarnaast werden er ook andere restrictie criteria bedacht; zo mochten patiënten geen drugs meer gebruiken, geen alcohol consumeren en geen co-infectie hebben met hepatitis B of HIV.

Impact van HCV

Een niet behandelde HCV infectie geeft een chronische ziekte die veel complicaties kan geven en uiteindelijk zorgt voor sterfte. Helaas is wereldwijd, in tegenstelling tot Nederland, behandeling nog voor Weinig mensen voorhanden vanwege de hoge kosten van de medicijnen en Weinig aandacht voor deze infectie. Daarnaast heerst er een groot stigma over de ziekte omdat het vaak voorkomt bij MSM maar ook bij injectorende drugsgebruikers.
HIV

Natuurlijk beloop
Het humaan immunodeficiëntie virus (HIV) is een infectie die de afweercellen (CD4-cellen) binnendringt en vernietigd. Hierdoor ontstaat er een verworven immunodeficiëntie syndroom (AIDS). Het CD4 aantal van iemand zonder HIV ligt tussen de 500 – 1500 cellen maar bij AIDS is dit onder de 200 cellen. Als gevolg kan het afweersysteem bepaalde infecties niet meer de baas zijn (opportunistische infecties) en zal een patiënt met AIDS hieraan overlijden. Infecties waaraan dan gedacht kan worden zijn bijvoorbeeld tuberculose, toxoplasmose, candidase, cryptokokkose, herpse simplex-virus (koortslipe) of varicellazostervirus (waterpokken/gordelroos). Daarnaast kunnen er ook verschillende vormen van kanker ontstaan zoals het kaposi sarcoom, ernstige baarmoederhals kanker of non-Hodgkin lymfomen.

Voorkomen en verspreiding
Wereldwijd zijn er ongeveer 38 miljoen mensen besmet met HIV en komen er jaarlijks 1,7 miljoen bij. Net als bij HCV zijn er grote verschillen tussen de HIV prevalentie over de verschillende werelddelen. Dit heeft ook bij HIV te maken met de verschillende verspreidingsroutes, maar ook aan de geïmplementeerde maatregelingen om HIV te voorkomen. In de jaren 80, het begin van de HIV epidemicie, verspreide de infectie zich met name seksueel onder de MSM gemeenschap. In sub-Sahara Afrika begon de verspreiding onder heteroseksuelen of babies via hun moeders tijdens de zwangerschap, bevalling of door borstvoeding. Net als bij HCV kan HIV ook verspreiden via besmet bloed of naalden. Van alle mensen die op dit moment leven met een HIV infectie bevind zich 70% in sub-Sahara Afrika.

In Nederland en andere Europese landen komt HIV vooral voor onder MSM. Sinds 2000 was er gedurende een bepaalde periode een stijging te zien in het aantal nieuwe HIV infecties. Nieuwe HIV infecties in de MSM populatie zijn vaak gerelateerd aan seksueel risico gedrag zoals onveilige anale seks. Gelukkig is er onder MSM een groot bewustzijn over het oplopen van HIV en wordt er gerelmatig getest. Daarnaast is pre-exposure prophylaxis (PrEP), medicijnen om geen HIV te krijgen, beschikbaar voor deze populatie. Ook door meer voorlichting en het sneller starten ART daalde het aantal nieuwe HIV infecties in de afgelopen jaren.

Helaas is er ook een populatie in Nederland waarbij HIV infecties vaak laat worden gevonden. Dit komt met name voor onder niet-Westere migranten, heteroseksuelen of onder ouderen. Deze groep is zich vaak niet bewust van het risico wat ze hebben doorgemaakt of schamen zich voor een mogelijke diagnose.
Diagnostiek en behandeling

HIV kan op verschillende manieren worden aangetoond in het lichaam. De meest gevoelige methode is het aantonen van virale deeltjes door middel van een HIV-PCR. Deze virale deeltjes zijn al snel aanwezig in het lichaam, maar net als bij HCV is dit dure diagnostiek. Daarnaast kunnen er ook verschillende antigenen (van het virus) of antilichamen (afweer response) worden aangetoond vanaf 2-3 weken na het oplopen van HIV. Hoe eerder HIV gediagnostiseerd is hoe beter, aangezien het dan minder lang het afweersysteem heeft aangevallen. De acute fase van HIV verloopt echter vaak assymptomatisch of mensen hebben griepere klachten waardoor er vaak niet aan HIV wordt gedacht.


Impact van een HIV infectie

Een HIV diagnose is voor veel mensen erg ingrijpend. Vaak is er schaamte rondom de diagnose, die leidt tot sociale isolatie of depressieve gevoelens. Verder ervaren mensen ook stigma uit hun omgeving. Aangezien HIV niet kan worden genezen zijn patiënten levenslang gebonden aan ART. Dit kan weer een grote invloed hebben op het dagelijks leven omdat het dagelijks innemen een constante herinnering is aan de HIV diagnose. ART heeft bijwerkingen of kan toxiciteit geven welke kan zorgen voor hart en vaatziekten, nier problemen, hoger cholesterol of osteoporose. Verder kan er de angst zijn om toch AIDS te krijgen. Ook is het hebben van HIV, ondanks goede onderdrukking van het virus, ook gerelateerd aan het sneller ouder worden (‘ageing’). Verder zijn er jaarlijkse ziekenhuis controles nodig. Alles bij elkaar zorgt dit ervoor dat de kosten en ziektelast voor HIV enorm zijn.

Eliminatie van HCV en de ziekte last van HIV

Zoals hierboven beschreven is de ziektelast van HCV en HIV enorm. Naast dat er voor beide virale infecties een aanzienlijk aantal mensen besmet zijn is de behandeling van HCV duur en die van HIV levenslang. Dit zorgt er ook voor dat beide infecties een enorme kostenbelasting zijn voor de zorg. Het elimineren van HCV als ziekte en de ziektelast van HIV zal dan ook zorgen voor een goede gezondheid en welzijn en verminderen van zorgkosten. Zowel de Wereld Gezondheids Organisatie (World Health Organization – WHO) als UNAIDS hebben eliminatie doelen gesteld voor HCV en HIV. De WHO streeft hierbij
naar een daling van 90% van de nieuwe HCV infecties en 65% van de HCV gerelateerde sterfte in 2030. De UNAIDS doelen streven naar 90% van de HIV-geïnfecteerden is bekend met hun diagnose, 90% van die groep ontvangt ART behandeling, en van de mensen op ART behandeling heeft 90% een onderdrukt virus. Deze doelen moeten behaald zijn in 2020 en worden verhoogd naar 95% in 2030. Het opstellen van deze doelen heeft ervoor gezorgd dat er besef bestond onder verschillende belanghebbende partijen over de urgentie en omvang van deze epidemieën. Vervolgens werden er plannen gemaakt om deze doelen te bewerkstelligen. Ondanks de grote inzet zijn tot de dag van vandaag nog heel veel mensen onwetend over hun besmetting en velen niet behandeld.

Nederland is goed op weg om beide doelen te bewerkstelligen. Een eerste stap daarin was het beschikbaar maken van DAAs voor alle HCV geïnfecteerden. De UNAIDS 90/90/90 doelen voor HIV zijn inmiddels behaald. Echter is er nog steeds een populatie laat in zorg en is er ook meer aandacht nodig voor het leven met HIV als chronische ziekte. Dit proefschrift beoogt dan ook bij te dragen aan de eliminatie van ziekte en ziektekosten in het kader van de WHO en UNAIDS 2030 eliminatie doelen.

Dit proefschrift

Dit proefschrift bestaat uit twee verschillende virussen; het geneesbare HCV en chronische HIV. De eerste twee delen van dit proefschrift gaan over de eliminatie en belemmeringen voor HCV eliminatie. Meer specifiek wordt dit gedaan door verschillende behandelingen- en monitorings strategieën te bekijken waarbij naast gezondheidswinst ook gekeken wordt naar een kostenreductie. Daarnaast wordt de HCV epidemiologie beter in kaart gebracht om hoog-risico groepen te ontdekken en wordt DAA resistentie bekeken. Het derde deel van dit proefschrift gaat over het verlagen van die ziekte last van HIV. Ondanks dat Nederland de UNAIDS 90/90/90 doelen heeft behaald, is de helft van de HIV geïnfecteerde mensen nog steeds laat in zorg. Naast dat late presentatie een hogere morbiditeit en mortaliteit heeft, is het ook nadelen voor de eliminatie doelen omdat HIV transmissie nog kan plaatsvinden. Late presentatie is een wereldwijd probleem en meer inzicht hierin is daarom belangrijk. Deel drie van dit proefschrift bekijkt welke soort patiënt zich laat in zorg presenteert en welke extra kosten dit met zich mee brengt. Verder wordt gekeken naar de impact van HIV op de kwaliteit van leven.

In hoofdstuk 2 worden verschillende HCV behandelijk strategieën besproken onder HIV geïnfecteerde MSM. Er wordt gekeken naar het effect van gelijk behandelen met DAAs ten opzichte van wachten tot klaring, of tot F2 fibrosis. Als uitkomstmaat kijken we naar de daling van het aantal nieuwe HCV infecties, het totale aantal HCV infecties en het
voorkomen van hepatocellulaire carcinomen. Daarnaast bekijken we de totale kosten van de verschillende strategieën. De uitkomsten van Hoofdstuk 2 laten zien dat het gelijk behandelen van nieuwe HCV infecties in deze populatie niet alleen kosten bespaart maar ook een gezondheidswinst oplevert.

Voordat een behandeling kan worden gestart moet een HCV infectie gediagnostiseerd zijn. Helaas zijn er nog veel mensen onwetend over hun HCV infectie wat nadelig is voor de WHO doelen. Voor nieuwe HCV infecties is de huidige manier van HCV diagnostiek suboptimaal waardoor HCV transmissie voortduurt. De zeer gevoelige HCV-PCR zou deze infecties wel oppikken. Echter is deze test een stuk duurder.

In hoofdstuk 3 worden verschillende monitorings strategieën besproken. Hierbij wordt vaker getest en verschillende testen gebruikt zoals de ALT, de HCV-PCR, en de HCV-core antigeen (HCV-cAg). De HCV-cAg is een test vergelijkbaar met de HCV-PCR alleen een stuk goedkoper. Naast dat alle HIV-geïnfecteerde MSM met deze testen worden getest, worden strategieën toegespitst op een sub-groep. De sub-groep bestaat uit HIV geïnfecteerde MSM die eerder een HCV infectie hadden. Dit omdat HCV reinfecties veel voorkomend zijn vanwege het vaak voortdurende hoog-risico gedrag. Er is in deze sub-groep dan ook een hogere voorafkans om HCV infecties te vinden. Hoofdstuk 3 concludeert dat het gebruik van de HCV-cAg test in een subgroep zowel het aantal infecties verlaagt als kosten reduceert in vergelijking tot het huidige testbeleid van monitoren met ALT. Daarnaast bespaart het kosten vergeleken met het gebruik van de HCV-PCR bij risicogedrag zoals de richtlijnen aangeven.

Nadat in 2015 de DAAs beschikbaar kwamen werd in Nederland al snel besloten dat iedereen toegang had tot deze medicijnen, dit in tegenstelling tot andere landen. In 2016 werd er dan ook een forse daling van het aantal nieuwe HCV infecties onder HIV-geïnfecteerde MSM waargenomen. Ondanks deze daling lieten de modellen uit hoofstuk 2 en 3 geen volledige HCV eliminatie zien in Nederland. Meer inzicht in de HCV epidemie is daarom van belang.

In hoofdstuk 4 wordt er gekeken naar de transmissie dynamiek van nieuwe HCV infecties in de periode voordat DAAs voor iedereen beschikbaar waren en de periode daarna. Door middel van fylogenie, een techniek die een stamboom maakt van het virus, wordt de verspreiding van HCV onder MSM in Nederland in kaart gebracht. Wat opviel uit deze resultaten was dat de epidemie bestaat uit een aantal grote clusters. Deze clusters bleven aanwezig ondanks een daling van het aantal nieuwe HCV infecties in Nederland. Uit hoofdstuk 4 kunnen we concluderen dat de HCV epidemie in Nederland geschikt is om gerichtere eliminatie strategieën op toe te passen. Dit houdt in dat bepaalde subgroepen vaker getest worden zoals besproken in hoofdstuk 3 of mee doen in risico reductie.
programma’s. Daarnaast zijn er sterke aanwijzingen dat de Nederlandse HCV epidemie onder MSM verweven is in een groter Europees netwerk waardoor meer onderzoek hiernaar sterk wordt aangeraden. Ook werden in clusters zowel infecties gezien van HIV-geïnfecteerde maar ook HIV-ongeïnfecteerde MSM waardoor we aanraden dat er meer aandacht moet komen voor HCV in de laatste groep.

Toen de DAAs net op de markt waren waren er nog veel onduideijkheden over de invloed van resistente. Wel was bekend dat er een aantal mutaties (RAS) waren die de genezingskans met de DAAs verlaagden. Dit zou erg nadelig zijn in het kader van eliminatie. Deel twee van dit proefschrift onderzoekt dan ook of resistentie een barrière is in het behalen van de eliminatie doelen.

In hoofdstuk 5 beschrijven we waarom een HCV resistentie surveillance van belang is in relatie tot het behalen van de WHO 2030 doelen. Concluderend heeft een resistentie surveillance een meerwaarde omdat er nog weinig over resistentie en het effect van resistentie bekend is. Het samenvoegen van data wordt aanbevolen om een beter beeld te krijgen van de omvang van het probleem en klinische relevantie. Daarnaast kan een dergelijke surveillance ook gebruikt worden voor real-time fylogenie, zoals besproken in hoofdstuk 4, wat kan bijdragen aan de bestrijding van transmissie.

Hoofdstuk 6 beschrijft het voorkomen van de RAS M28V die voorkomt in een groot gedeelte van de MSM populatie in Nederland. Ondanks dat deze HCV variant weinig effect heeft op onze huidig gebruikte DAA combinaties, is er wel een effect redutie gevonden tegen andere DAA combinaties. Deze combinaties worden met name nog gebruikt in landen met weinig financiële middelen. De snelle verspreiding van deze variant in onze populatie benadrukt het belang van een resistentie surveillance zoals besproken in hoofdstuk 5. Verder werd deze HCV variant ook gevonden in een MSM populatie in Frankrijk wat de hypothese dat er een Europees netwerk onder MSM bestaat benadrukt.

In het derde deel van dit proefschrift wordt de chronische infectie HIV besproken in het kader van de UNAIDS eliminatie doelen. Nederland is een land waarbij de 90/90/90 doelen van de UNAIDS al behaald zijn. Echter presenteren zich nog steeds 50% van de mensen met een nieuw infectie zich laat in zorg idem aan andere Europese landen. Late presentatie is geassocieerd met hoge morbiditeit, mortaliteit en het mogelijk voortzetten van de verspreiding van HIV.

Hoofdstuk 7 bekijkt de kosten van een HIV infectie over een periode van vijf jaar na het starten van ART. Hierbij wordt een verdeling gemaakt tussen de verschillende momenten van presentatie; 1) mensen die op tijd in zorg komen (CD4 >350), 2) mensen die laat in zorg
Hoofdstuk 7 laat zien dat de hoogste kosten worden gegenereerd door het gebruik van ART. Opvallend is dat late of zeer late presenteerders hogere niet-ART kosten (co-medicatie, ziekenhuisopnames, polikliniek bezoeken en HIV gerelateerde testen) hebben dan mensen die zich op tijd presenteerden. Deze hoge kosten zijn tot vijf jaar na start van ART nog zichtbaar. Factoren gerelateerd aan late presentatie zijn; oudere leeftijd, heteroseksuele transmissie route en niet-Nederlandse afkomst.

Hoofdstuk 8 bekijkt de kwaliteit van leven van HIV-geïnfecteerde mensen. Dit is een belangrijk onderwerp aangezien mensen met een HIV infectie een zelfde levensverwachting hebben als mensen zonder HIV infectie. Daarmee is HIV een chronische infectie geworden waarbij kwaliteit van leven hoog in het vaandel moet staan. In hoofdstuk 8 wordt een vergelijking gemaakt van HIV geïnfecteerde mensen uit Nederland en Engeland met de ongeïnfecteerde bevolking. Onze studie vond een haast vergelijkbare kwaliteit van leven van mensen met HIV en mensen zonder HIV. Echter werd er in beide landen met name een hogere last gezien van angst en depressie. Dit toont aan dat hier meer aandacht voor moet komen binnen de HIV zorg. Daarnaast vinden wij dat kwaliteit van leven moet worden toegevoegd als een vierde 90 aan de UNAIDS doelen.

In hoofdstuk 9 van dit proefschrift bespreken we de inzichten die zijn vergaard met de bovenstaande onderzoeken. Er zijn een aantal aanbevelingen die naar mijn mening belangrijk zijn in het kader van de WHO en UNAIDS doelen en nieuwe virale epidemieën. Als eerste moeten HCV infecties zo snel mogelijk behandeld worden, niet alleen in de MSM populatie. Hierbij is een duidelijke gezondheidswinst die voorop moet staan, maar daarnaast ook een kosten reductie. Verbeterde en versimpelde diagnostiek, zoals sneltesten, is essentieel om veel mensen makkelijk en vaak te kunnen testen. Dit moet ook thuis kunnen gebeuren, in een seksclub of andere locatie waar de doelgroep zich bevindt of stigma minder wordt ervaren. Naast dat dit belangrijk is voor HCV geldt dit ook voor andere virale ziektes, zoals HIV of SARS-CoV-2. Ten tweede kunnen surveillances van HCV infecties bijdragen aan het opsporen van resistentie, maar ook nieuwe transmissie events opsporen. In populaties waar veel transmissie plaatsvindt kan vaker worden getest of zijn risico reducerende programma’s gewenst. Ook hier geldt dat de zelfde technieken kunnen bijdragen in het beperken van de transmissie bij andere virale infecties. Daarnaast kan een robuust surveillance programma ook snel een nieuwe mutant detecteren, zoals die van SARS-CoV-2 in het Verenigd Koninkrijk. Ten derde kan kunstmatige intelligentie, zoals neurolinguïstisch programmeren, context uit medische dossiers analyseren en richting geven aan patiënten met risico gedrag of signalen van een HCV/HIV infectie. Ten vierde is intergratie en decentralisatie van de zorg belangrijk. Integratie kan processen vergemakkelijken omdat er al een bestaande structuur is. Daarnaast kan het ook kosten...
besparen. Decentralisatie van zorg naar bijvoorbeeld de huisarts kan zorgen voor een verhoogde toegankelijkheid van de zorg en ook kosten besparen. Als laatste is er een grote rol voor E-health en apps, in de toekomst van de zorg. In de zorg voor chronische ziekten zouden patiënten hun kwaliteit van leven kunnen melden via een app en zo kan er worden besloten tot meer of minder consulten. Dit kan de eerste stap zijn in een meer gepersonaliseerde zorg.
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ABOUT THE AUTHOR
About the author

Stephanie Popping was born on September 28th, 1988 in Zoetermeer, the Netherlands. As a little girl she always dreamed about becoming a Doctor of Medicine. This dream became reality when she was admitted at the Erasmus Medical Center (Erasmus MC) in Rotterdam for her medical training. During her medical training she developed an excessive interest for infectious diseases. She participated in a tropical medicine course and performed internships specialized on infectious diseases at the University of Stellenbosch in South Africa and the Heartlands University Hospital Birmingham in the United Kingdom. She obtained her Doctor of Medicine degree by August 2015 at the Erasmus MC and decided that the next step in her career would be a PhD-research. In November 2015, she initiated her PhD-research, entitled “Elimination of disease and burden of disease” under the supervision of Prof. Dr. A. Verbon, Prof Dr. C. A. B. Boucher, and Dr. D. A. M. C. van de Vijver at the Department of Viroscience of the Erasmus MC. During her PhD she established and coordinated a Hepatitis C antiviral resistance database (HepCare) and participated in the global SHARED project. Additionally, she is a member of the CMV resistance working group, a participant of the EuResist Med School, where HIV resistance is researched, and involved in the implementation of Valued Based HealthCare. In September 2020 Stephanie started her specialization in medical microbiology at the Medical Microbiology and Infectious Diseases department at the Erasmus MC. She lives happily with her husband and two girls in a place with a lot of green and quietness.
PUBLICATIONS AND PHD PORTFOLIO
Publications


6. Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2): an open-label, multicentre, single-arm, phase 3b trial

7. Emergence and Persistence of Letermovir-Resistant Cytomegalovirus in a Patient with Primary Immunodeficiency
Popping S, Dalm VASH, Lübke N, Cristanziano VD, Kaiser R, Boucher CAB, Van Kampen JJA

8. Targeted HCV core antigen monitoring among HIV-positive men who have sex with men is cost-saving
*J Virus Erad.* 2019 Nov 4;5(4):179-190

9. Transmission of NS5A-Inhibitor Resistance-Associated Substitutions Among Men Who Have Sex with Men Recently Infected with Hepatitis C Virus Genotype 1a
*Clinical Infectious Diseases,* Volume 71, Issue 8, 15 October 2020, Pages e215–e217

10. The case for simplifying and using absolute targets for viral hepatitis elimination goals
Polaris Observatory Collaborators
*J Viral Hepat.* 2021 Jan;28(1):12-19

11. Persistent transmission of HCV among men-who-have-sex-with-men despite widespread screening and treatment with direct-acting antivirals
*Manuscript submitted for publication*
12. Quality of life among people living with HIV in England and the Netherlands comparable to the general population  
*Manuscript submitted for publication*

13. Characteristics and short- and long-term direct medical costs of those presenting late and very late for HIV care in the Netherlands  
*Manuscript submitted for publication*

14. Cost-effectiveness of introducing Direct Acting Antivirals-based treatment immediately after diagnosis to reduce Hepatitis C incidence among HIV positive MSM in Thailand  
Mukherjee S, Colby D, Ramataursing R, **Popping S**, Sriplienchan S, Chinbunchorn T, Phanuphak N, van de Vijver D  
*Manuscript submitted for publication*

15. The global prevalence of resistance associated substitutions (RASs) in “unusual” HCV subtypes  
**S. Popping**, S.Fourati*, AYM Howe, VC Di Maio, A. de Salazar, C. Rodrigo, R.J de Knecht, M. Kjellin, J. Lennerstrand, M. Douglas, F. Ceccherini-Silberstein, P.R. Harrigan, F. Garcia, C. Boucher, JM Pawlotsky* on behalf of the contributing members of the SHARED database  
*Manuscript in preparation*

*Equally contributed*
PhD portfolio

Name PhD student: Stephanie Popping

Erasmus MC Department: Viroscience

PhD period: 01/11/2015 until 29/03/2020

Promotor: Prof. dr. C.A.B Boucher

Prof. dr. A. Verbon

Education: Gymnasium – Zuyderzee college Emmeloord

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**Prevalence of NS3 and NS5A Resistance Associated Substitutions through European DAA-Failures**

European Workshop of HIV and Healthy Living - Barcelona

Country specific factors determine the quality of life among people with HIV in two western European countries

ARREVIR GenFor meeting, Invited speaker - Cologne

CMV diagnostics in immunocompromised patients

17th European meeting on HIV & Hepatitis - Rome

The transmission dynamics of acute HCV infections in HIV-positive men who have sex with men in the Netherlands is suitable for targeted risk reduction strategies

12th Netherlands Conference on HIV (NCHIV) – Amsterdam

Substantial transmission of the M28V resistant associated substitution among acute HCV/HIV co-infected MSM

AASLD – The Liver Meeting - Boston

The Global Prevalence of Resistance Associated Substitutions (RASS) in “Unusual” HCV Subtypes

The Asian Pacific Association for the Study of the Liver (APAS) - Manilla

Characteristics of resistance-associated substitutions in unusual hepatitis C virus (HCV) subtypes

Erasmus MC, Bridge meeting

Substantial transmission of the M28V resistant associated substitution among acute hepatitis C HIV co-infected MSM

Poster

9th Netherlands Conference on HIV (NCHIV) – Amsterdam

Feasibility and results of the EuroQol 5-dimension quality of life questionnaire among HIV-positive individuals at an outpatient clinic

22nd International AIDS conference - Amsterdam

Late presenters drive the non-ART cost of HIV-care

AASLD – The Liver Meeting – San Francisco

The prevalence of hepatitis C virus NS5A polymorphisms in Europe

23rd International Bioinformatics Workshop on Virus Evolution and Molecular Epidemiology (VEME) (Berlin)

The origin of acute HCV in HIV-infected men who have sex with men in the Netherlands

17th European meeting on HIV and Hepatitis (Rome)

Timely emergence of letermovir resistance in a patient with primary immunodeficiency – the need for resistance surveillance
### Attended conferences and symposia

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### Teaching activities

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<td>Activity</td>
<td>Year</td>
<td>ECTS</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Lecture “Hepatitis C and different monitoring strategies” – Master</td>
<td>2016</td>
<td>0.2</td>
</tr>
<tr>
<td>Infection &amp; Immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lecture “Chemsex” – Minor Infectious diseases (2016-2020)</td>
<td>annualy</td>
<td>0.6</td>
</tr>
<tr>
<td>Viruskenner coach</td>
<td>2016-2018</td>
<td>2.0</td>
</tr>
<tr>
<td>Lecture “Statistics” – Honours class</td>
<td>2018</td>
<td>0.2</td>
</tr>
<tr>
<td>Coaching bachelor students (7 students) in year 1, 2, and 3 of medical</td>
<td>2015-2019</td>
<td>4.0</td>
</tr>
<tr>
<td>training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supervision master thesis: Evelien Stempher</td>
<td>2019</td>
<td>2.0</td>
</tr>
<tr>
<td>Health-related quality of life among people living with HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection and Immunity phylodynamics tutor</td>
<td>2019</td>
<td>0.5</td>
</tr>
<tr>
<td>Supervision honours class student: Lisbeth Versteeg</td>
<td>2019-2020</td>
<td></td>
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</table>

**Awards and travel grants**

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd European workshop on HIV &amp; Healthy Living - Young Investigator grant</td>
<td>2016</td>
</tr>
<tr>
<td>American Association for the Study of Liver Diseases Foundation</td>
<td>2018</td>
</tr>
<tr>
<td>2018 Early Career Investigator Award in Clinical/Translational Science</td>
<td></td>
</tr>
<tr>
<td>4th European workshop on HIV &amp; Healthy Living - Young Investigator grant</td>
<td>2019</td>
</tr>
<tr>
<td>International Liver Conference, - EASL Young Investigator Award</td>
<td>2019</td>
</tr>
<tr>
<td>European meeting on HIV &amp; Hepatitis – Young Investigator grant</td>
<td>2019</td>
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**Other**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Year</th>
<th>ECTS</th>
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<tbody>
<tr>
<td>ESAR meeting Rome – HepCare project introduction</td>
<td>2016</td>
<td>0.1</td>
</tr>
<tr>
<td>15th HCV DrAG meeting (HCV resistance working group)</td>
<td>2016</td>
<td>0.1</td>
</tr>
<tr>
<td>USMLE S.O.S– preparation course</td>
<td>2016</td>
<td>0.5</td>
</tr>
<tr>
<td>EuResist Medschool participant – Bioinformatics &amp; antiviral resistance</td>
<td>2018</td>
<td>2.0</td>
</tr>
<tr>
<td>Medical Business Masterclass Roadshow</td>
<td>2019</td>
<td>1.0</td>
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<tr>
<td>E-Module – as part of “Basis Kwalificatie Onderwijs”</td>
<td>2020</td>
<td></td>
</tr>
</tbody>
</table>
DANKWOORD
We must find time to stop and thank the people who make a difference in our lives

*JFK*
Dankwoord

There are many great people I want to thank for their support, inspiration, and effort during my PhD journey.

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