

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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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

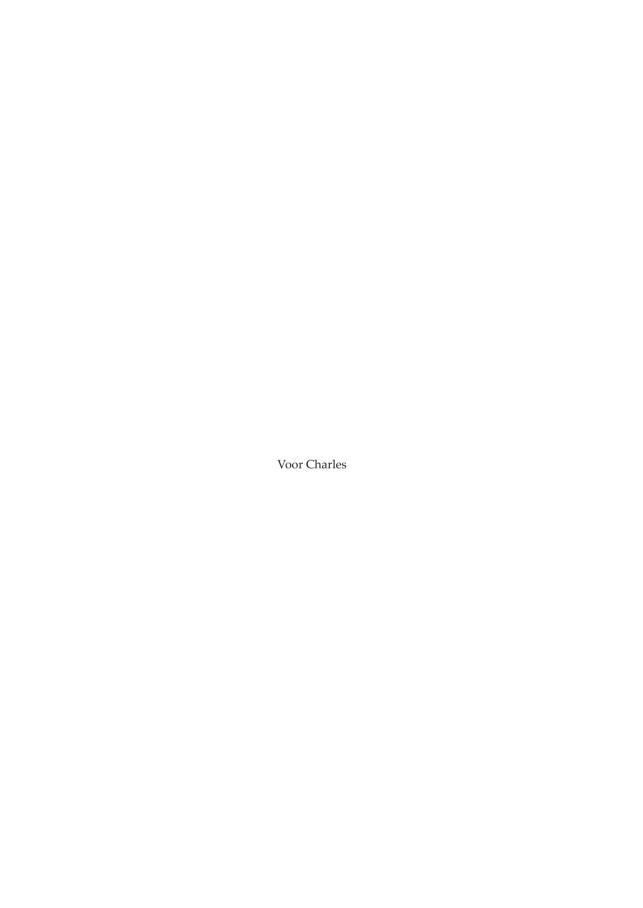
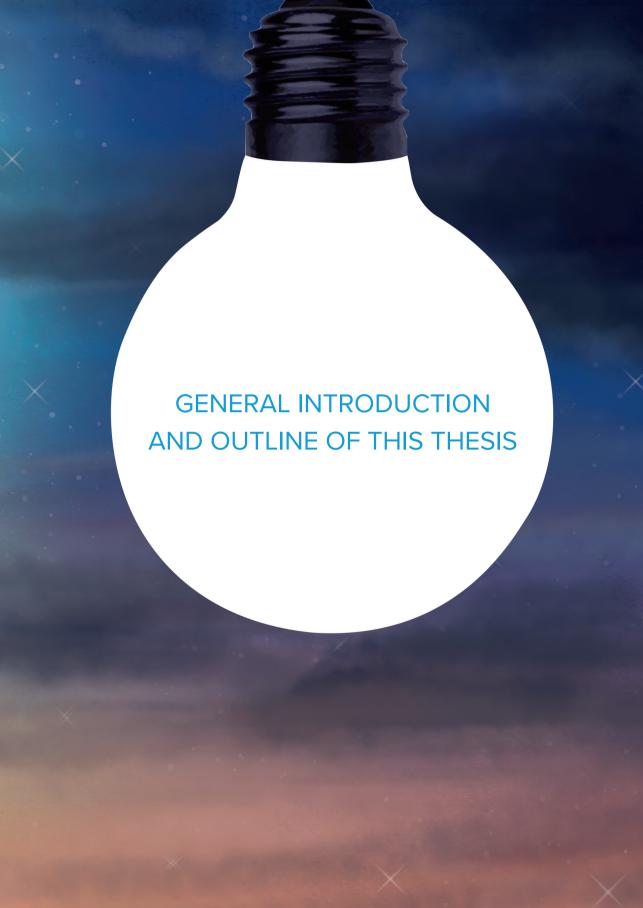


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Partly based on

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

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

<u>And</u>

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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. HCV is estimated to infect 71 million people, which is ~1% of the total global population. In contrast to most other communicable diseases, the absolute burden of disease has increased in the past couple of years.

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 2030⁴. 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.⁴ 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.¹⁶ Remarkablye, 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.¹⁷ 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.^{16,18-20}

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. 22

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.^{23,24} Nevertheless, many countries have limited harm-reduction programs due to ongoing concerns (despite evidence to the contrary) that such initiatives may boost drug use.^{24,25} 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 ²⁶. 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.⁹

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/ μ L. 27,28

Globally, an estimated 38 million people are living with HIV and this number increases annually by ~2 million new HIV infections.²⁹ 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.^{30,31} 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.²⁹ The earlier ART is initiated after the initial HIV infection, the lower the damage inflicted to the immune system.^{32,33} Early ART initiation also has public health benefits as PWLH 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.³⁴⁻³⁷

Owing to the successes of good ARTs PLWH may have a comparable life-expectancy as to the general population.³⁸⁻⁴⁰ 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. 41-43 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 supressed there is an association with early ageing, frailty, and HIV-related neurocognitive impairment, all which require specialized and additional care. 44-47 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. In the Netherlands.

HCV monitoring is embedded in HIV-care through annual HCV-antibodies and biannual ALT monitoring.⁵⁷ 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.⁵⁸

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.⁵⁹ 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.^{60,61}

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 $< 350 \mu$ L 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. 10,63 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 2030.²⁹ 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 focuses 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.

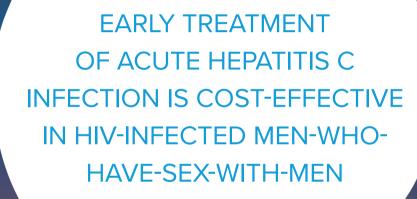
Part 2 aims to investigate if resistance to DAAs proposes a barrier towards HCV elimination. **Chapter 5** outlines why DAA resistance can jeopardize HCV elimination efforts and that resistance surveillance is essential to measure the effect and occurence of resistance. Chapter 6 shows the rapid spread 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



Stephanie Popping, Sebastiaan Hullegie, Anne Boerekamps, Bart Rijnders, Robert de Knegt, Jürgen Rockstroh, Annelies Verbon, Charles Boucher, Brooke Nichols, David van de Vijver

PLoS One. 2019 Jan 10;14(1)

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 OALYs.

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 ϵ 68.3 and ϵ 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 ϵ 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.^{7,8} 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.58,64 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 2030.4

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.⁶⁵ 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). 66,67 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.⁶⁸ MSM are at high-risk of acquiring HCV due to high-risk sexual behaviour, including an excessive number of partners combined with drug use.⁵⁴ In the Netherlands, contrary to many other countries, no new HCV infections are reported among injecting drug users (IDU). 55,56 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).^{48,58} 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). 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 OALY 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. 100,101 For this study, we used a willingness-to-pay threshold of €20,000 per QALY. 100,102

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

Model Parameters of HCV transmission model among	Range/number (median)	
Dutch MSM	t = calibrated	
Annual HIV diagnoses among MSM per time-period		
2002-2014	720-740 ⁷³	
2015	62072	
2016	580	
Susceptible HIV-infected MSMs in 2002	3800	
Patients with HCV in 2002	2-10% ⁷⁶ †	
Mortality rate HIV patients ≥350 CD4 count	1/4582 *	
Transmissibility of HCV	0.01-0.05 †	
Diagnosed percentage per HCV testing moment	70-100%83,84	
Clearance rate	15-25%66,67,85	
Time to clearance	40-170 days ⁸⁵	
Reinfection rate	8-26.5%, per year ^{86,87}	
Time from transmission until treatment (acute HCV)	16.5 - 25 weeks ⁸⁸	
Time from transmission until treatment (F0 chronic)	20.4 - 54.2 weeks 88 \dagger Υ	
Patients in stage F3, F4 in 2002	10-30%	
HCC rate	2-5% 89,90	
Treatment parameters	Range/number	
SVR, DAA F0-F3	89-100% ^{6,91}	
Treatment duration F0-F3	12 weeks ⁹²	
SVR, DAA cirrhosis	80-95% 93	
Treatment duration F4 compensated and decompensated	16 weeks ⁹⁴	
Re-treatment duration F0-F3	12 weeks ⁹²	
Re-treatment duration F4 compensated and decompensated	16 weeks ⁹⁴	
Quality of Life	Utility score	
HIV mono-infection	0.94^{95}	
Acute HCV infection	0.84^{88} §	
HCV F0-F3 stage	$0.84^{96}~\S$	
Compensated cirrhosis	$0.38 \text{-} 0.67^{97}$	
Decompensated cirrhosis	0.38^{97}	
DAA based therapy	0.84^{88} §	

Table 1. Continued

Model Parameters of HCV transmission model among Dutch MSM	Range/number (median) †= calibrated	
Costs	Price in €	
Doctors visit	13698	
HCV RNA	105 - 225 [¶]	
HCV genotype	130 - 252 ¶	
Ultrasound of the liver	90 - 226 [¶]	
Biochemistry and liver function tests	38 – 46 ¶	
F3 additional costs per year **	808 ¶	
F4 additional costs per year **	808 ¶	
DAA regimen 12 weeks	35,000 ¶	

Abbreviations: HCV: hepatitis C virus, MSM: men having sex with men, SVR: sustained virological response, PEG-IFN: PEGylated interferon, RBV: ribavirin, DAA: direct-acting antiviral

¥ Weeks are based on the time that a patient needs to be diagnosed (16.5-25 weeks88) 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.88 In addition, an HIV-infected MSM with CD4 >350 cells/µl has a life expectancy of 80 years.82 Therefore, we used a 40-year time horizon to calculate the epidemiological impact and economic outcomes.¹⁰³ 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 preexposure prophylaxis (PrEP) and the impact of continuing transmission from undiagnosed HCV-infected individuals (up to 100 individuals that remain undiagnosed).¹⁰⁴ HIV PrEP

^{*} 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

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.^{77,105-107} 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

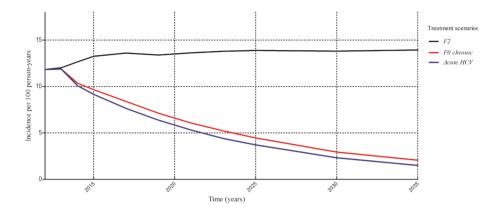
Before 2015 there was a stabilizing incidence of 1.2/100 person-years and prevalence of 5.0%. After starting our treatment scenarios, the model projected an increasing, but further stabilizing incidence at 1.4/100 person-years (IQR 1.2-1.7) for the delayed F2 treatment scenario after 20 years. The prevalence 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).



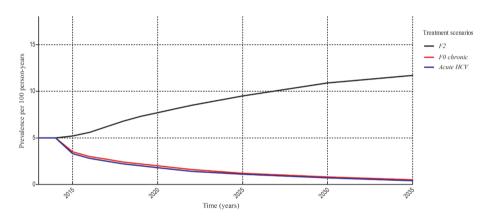


Fig 1. Short-term epidemiological hepatitis c virus impact among HIV-infected MSM

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 2. Results of the main cost-effectiveness analysis of three different DAA treatment scenarios

Scenario*	HCV infections	HCV Prevalence	Total costs,	
	averted at 40yr	reduction at 20yr	Euro's € (millions)	
F2	-	-	€ 98.4	
F0 acute	7457	97%	€ 68.3	
F0 chronic	7070	96%	€ 75.1	

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 \notin 98.4 million (IQR \notin 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, \notin 68.3 million (62.9 – 75.1) and \notin 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 \notin 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 ϵ 6,348 per QALY gained for annual testing.

QALY	Incremental costs	Incremental QALYs	ICER
x 1000	Euro's € (millions)		
331.3	-	-	-
334.7	-€ 30.0	3425	cost saving
334.6	€ 6.9	-47	dominated

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.

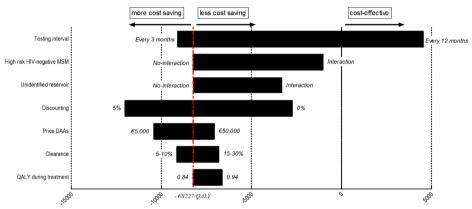


Fig 2. One-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) (€/QALY) of DAA treatment

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

Abbreviations: DAA: direct-acting antivirals, ICER: incremental cost-effectiveness ratio, MSM menwho-have-sex-with-men.

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. ¹⁰⁸ Restrictions can be based on fibrosis, co-infection and substance abuse. ^{92,109,110} Still, countries continue to delay DAA treatment until F2 or even F3 stages. ^{110,111} 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. 112,113 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. 114

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.^{64,115} 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.^{6,116,117} 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 recommend 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.^{55,56} 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

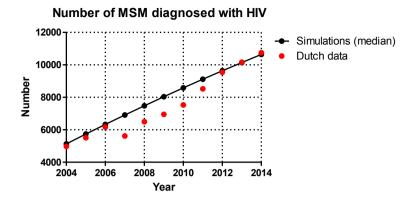
Conclusion

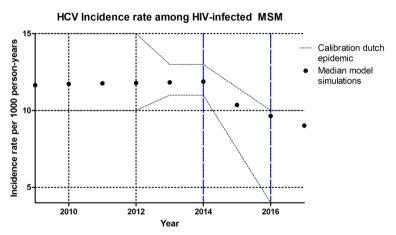
In conclusion, our study shows that DAA treatment for acute HCV-infected individuals is a cost-saving prevention approach that strongly reduces the HCV epidemic among HIV-infected MSM, despite high reinfection rates. Furthermore, shows our study that although earlier treatment (F0 chronic) is dominated 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

Parameter used to accept simulations	Values accepted
Number of HIV-HCV co-infections in 2014	450-850 ⁴⁹
Annual number of new HIV-HCV co-infections (2014)	$100-150^{48}$
Incidence rate in 2012 through 2014	11-13 per 1,000 person-years ⁵⁰
Incidence rate after DAA roll-out 2016	$4 - 10 \text{ per } 1000 \text{ person-years}^{77,120}$
Reinfection rate in 2014	8 – 26.5% per year ^{51,71}



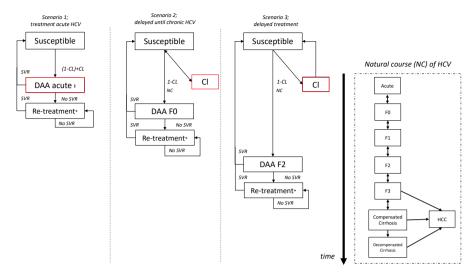


S1 Fig. Calibration figures

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).58

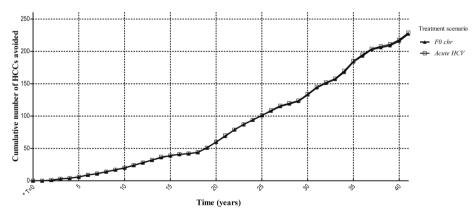
S2 Table. Parameters in the model

Parameters of epidemic among HIV-infected MSM	Range [source/rationale]		
Annual new sexual partners	[Calibrated]		
Highest risk group	20-100		
Risk group 2	5-15		
Risk group 3	1-4		
Risk group 4	0.1 – 0.9		
Proportion per risk group	[Calibrated]		
Highest risk group	-0.14		
Risk group 2	0.2		
Risk group 3	0-0.3		
Risk group 4 0.4-0.9			
Rate of assortative mixing 0-0.8 [Calibrated]			
Patients in stage F3, F4 in 2002	10%-30% [Calibrated]		
Life Expectancy and mortality			
HIV-infected men CD4>350	80 years ⁸²		
HIV/HCV co- infected (F0-F3stage)	80 years ⁸²		
HIV/HCV co-infected compensated cirrhosis	0.024-0.055 per year ¹²¹		
Life expectancy HIV/HCV decompensated cirrhosis 0.019-0.35 per year ¹²			
Disease progression			
F0 to F1	0.098 - 0.122, per year ⁸¹		
F1 to F2	0.095 - 0.140, per year ⁸¹		
F2 to F3	0.097 - 0.159, per year ⁸¹		
F3 to Compensated cirrhosis	0.098 - 0.135, per year ⁸¹		
Compensated to decompensated cirrhosis	0.029 - 0.063, per year ¹²¹		
Compensated to decompensated cirrhosis	0.029 - 0.063, per year ¹²¹		
Cirrhosis to Hepatocellular carcinoma	0.01 - 0.03, per year ¹²²		
Transplantations	0 per year		
Additional cost to delayed treatment stage			
Cost of HCC (including hospitalization, treatment, surgery, and	€67.591 – €233.573 per		
care until death)	patient123,124		



S2 Fig. Simplified diagram capturing the HCV transmission model among HIV-infected MSM evaluating different treatment scenarios

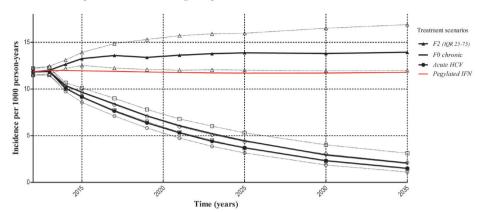
Individuals can be treated during an acute HCV infection (Scenario 1), treatment is delayed until possible spontaneous clearance (Scenario 2), or individuals are treated according to the delayed F2 treatment scenario (Scenario 3). Individuals progress through the natural course of disease over time Abbreviations: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

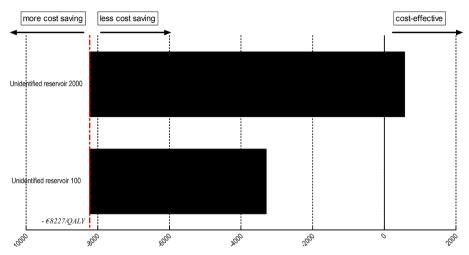
Hepatitic C incidence among HIV positive men who have sex with men



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 pegylatedinterferon 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.

One-way sensitivity analysis of the incremental cost-effectivenss ratio (€/Qaly)



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

Variable	Description
S _i	Individuals not infected with HCV; sexual activity classes <i>i</i> =1-4
E_{i}	Entry rate HIV-infected MSM, sexual activity classes <i>i</i> =1-4
SPi	Individuals not infected with HCV that previously cleared HCV or were cured from HCV; sexual activity classes $i=1-4$
	HCV-infected individuals that are clearing HCV; sexual activity classes <i>i</i> =1-4 Different forms of clearing = n 1= clearing the virus and on treatment
Cli,n	2= clearing the virus and no treatment
	3= clearing the virus and no diagnosis 4 = clearing the virus before diagnosis B= after being infected
$\mathbf{F}_{\mathrm{i,j,m}}$	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
$Rx_{i,j,m,z}$	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
$N_{i,j,z}$	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 $z=2-3$
$C_{i,m}$	Patients with cirrhosis that are not infected with HCV, sexual activity classes i=1-4, m=1 reflects compensated cirrhosis, m=2 decompensated cirrhosis
HCC	The occurrence of a hepatocellular carcinoma over time

Input variables

The values for the input variables are given in table 1 of the main text.

Variable	Description
$\lambda_{_{\mathrm{i}}}$	Force of infection or the rate by which individuals become infected with HCV in
	sexual activity group <i>i</i> (i=1-4)
μ	Mortality
μ_{comp}	Mortality, compensated cirrhosis
μ_{decomp}	Mortality, decompensated cirrhosis
$1/\tau$	Time to HCV clearance
SVRj	Sustained Virological Response (SVR) in fibrosis stage of infection j (j is 1-4)
SVR_{PEG}	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
$\delta_{\rm j}$	duration of DAA treatment in stage of fibrosis j
$\delta_{ ext{PEG}}$	duration of pegylated interferon (only in the scenario's where DAAs are delayed until stage F2 or stage F3) during calibration
ф	proportion diagnosed with HCV
ε	Proportion receiving treatment in acute stage of infection E = 0 in delayed F2 scenario
Clear	Proportion clearing HCV
$\Theta_{\rm z}$	Time to start the zth course of DAA treatment; z=1, 2, 3
Δj, j+1	HCV progression rate by stage j=0-4
$\Delta_{\rm decomp}$	Progression rate from compensated to decompensated cirrhosis
χ	Percentage of patients that will develop an HCC over time
σ	Period to await spontaneous clearance to occur

Model equations

$$\frac{dSi}{dt} = E_i - S_i * (\lambda_i + \mu)$$

$$\frac{dSPi}{dt} = \tau * (CL_{i,2} + CL_{i,2 B} + CL_{i,13} + CL_{i,3B} + Clear) + \delta_{j} * (CL_{i,1 B} + CL_{i,1)} + \sum_{j=0}^{j=3} \sum_{z=1}^{z=2} Rx_{i,j,z} * SVR_{j} * \delta_{i} + Rx_{i,3,3} * \delta_{i} * SVR_{i} - Sp_{i} * (\lambda_{i} + \mu)$$

$$\frac{dCli,n}{dt} = \text{Clear*} \ \phi * \lambda_i * S_i * \varepsilon - \text{CL}_{i,13} * \phi * \varepsilon - \text{CL}_{i,1} * (\tau + \mu)$$

The following equations differ per scenario

immediate scenario 1)

$$\frac{\textit{dF i}.0.1}{\textit{dt}} = \phi * \epsilon * (1 - Clear) * \lambda_i * S_i + F_{i,0,3} * \phi * \epsilon - F_{i,0,1} * (\theta_z + \Delta_{0,1} + \mu)$$

$$\frac{dF i,0,1r}{dt} = \phi * \epsilon * (1 - Clear) * \lambda_i * SP_i - F_{0Reinf} * (\theta_z + \Delta_{0,1} + \mu)$$

2) the chronic treatment scenario

$$\frac{dF \, i.0.1}{dt} = \phi * \epsilon * (1 - \text{Clear}) * \lambda_i * S_i + F_{i,0,3} * \phi * \epsilon - F_{i,0,1} * \theta_z * \sigma + F_{i,0,1} (\Delta_{0,1} + \mu)$$

$$\frac{dF_{i,0,1}r}{dt} = \phi * \epsilon * (1 - Clear) * \lambda_i * SP_i - F_{0Reinf} * \theta_z * \sigma + F_{0Reinf} * (\Delta_{0,1} + \mu)$$

the delayed F2 scenario

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

$$\frac{dF i,0,1r}{dt} = \phi * \epsilon * (1 - Clear) * \lambda_i * SP_i - F_{0Reinf} * (\Delta_{0,1} + \mu)$$

$$\frac{dF i,1,}{dt} = (F_{i,0,1} + F_{i,0,2} + F_{i,0,1r} + F_{i,0,3}) * \Delta_{0,1} - Fi,1 * (\Delta_{1,2} + \mu)$$

$$\frac{dRx \, i,j,z}{dt} = F_{i,j} * \theta_z + N_{i,j,z} * \rho - Rx_{i,j} * (\delta_j + \mu) \text{ for } j = \{2,3\}, z = \{1,2\}$$

$$\frac{dN_{i,j,z}}{dt} = Rx_{i,j,z-1} * \delta_j * (1 - SVR_j) + N_{i,j-1,z} * \Delta_{j-1,j} - N_{i,j,z} * (\Delta_{j,j+1} + \theta_z + \mu) \text{ for } j = \{2,3\}, z = 2$$

Continuation of the model equations for all scenarios

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

$$\frac{dF \ i.0.2}{dt} = (1 - Clear) * (1 - \epsilon) * \phi * \lambda_i * (S_i + SP_i) + F_{i,0,3} * \phi * (1 - \epsilon) - F_{i,0,2} * (\Delta_{0,1} + \mu)$$

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

$$\frac{\mathit{dF}\:i,1,}{\mathit{dt}} = \left(F_{i,0,1} + F_{i,0,2} + F_{i,0,1r} + F_{i,0,3}\right) * \Delta_{0,1} - Fi,1 * \left(\theta z + \Delta_{1,2} + \mu\right) *$$

$$\frac{dF \, i,j}{dt} = F_{i,\,j-1} * \Delta_{j-1,j} - F_{i,j} * (\theta_{z} + \Delta_{j,j+1} + \mu) \text{ for } j = \{2,3\}$$

$$\frac{dF \, i, 4, 1}{dt} = F_{i,3} * \Delta_{3,4} - F_{i,4,1} * (\theta_z + \Delta_{decomp} + \mu_{comp})$$

$$\frac{dF i,4,2}{dt} = F_{i,4,1} * \Delta_{decomp} - F_{i,4,2} * (\theta_z + \mu_{decomp})$$

$$\frac{dRx \, i,j,z}{dt} = F_{i,j} * \theta_z + N_{i,j,z} * \rho - Rx_{i,j} * (\delta_j + \mu) \text{ for } j = \{0,1,2,3\}, z = \{1,2\}$$

$$\frac{dRx \, i,3,3}{dt} = N_{i,j,2} * \theta_z - Rx_{i,3,3} * (\delta_j + \mu)$$

$$\frac{dRx i,4,1,z}{dt} = F_{i,4,1} * \theta_z + N_{i,4,1,z} * \theta_z - Rx_{i,4,1} * (\delta_j + \mu_{comp})$$

$$\frac{dRx \, i,4,2,z}{dt} = F_{i,4,2} * \theta_z + N_{i,4,2,z} * \theta_z - Rx_{i,4,2} * (\delta_j + \mu_{decomp})$$

$$\frac{dN i.j.z}{dt} = Rx_{i.j.z-1} * \delta_j * (1 - SVR_j) - N_{i.j.z} * (\Delta_{j.j+1} + \theta_z + \mu)$$
 for j=0, z=2

$$\frac{dN i.j.z}{dt} = Rx_{i,j,z-1} * \delta_j * (1 - SVR_j) + N_{i,j-1,z} * \Delta_{j-1,j} - N_{i,j,z} * (\Delta_{j,j+1} + \theta_z + \mu) \text{ for } j = \{1,2,3\}, z=2 * \{1,2,3\}, z=2$$

$$\frac{dN i,3,3}{dt} = Rx_{i,3,3} * \delta_j * (1 - SVR_j) + N_{i,3,3} * (\Delta_{3,4} + \theta_z + \mu)$$

$$\frac{\mathit{dN}\,\mathit{i.4.1.z}}{\mathit{dt}} = Rx_{\mathit{i.4.1.z-1}} * \delta_{\mathit{j}} * (1 - SVR_{\mathit{j}}) + N_{\mathit{i.3.z}} * \Delta_{\mathit{3.4}} - N_{\mathit{i.4.1.z}} * (\Delta_{decomp} + \theta_{z} + \mu_{comp}) \text{ for } z = \{2.3\}$$

$$\frac{dN i.4.2.z}{dt} = Rx_{i,4,2,z-1} * \delta_j * (1 - SVR_j) + N_{i,4,1,z} * \Delta_{decomp} - N_{i,4,1,z} * (\theta_z + \mu_{decomp}) \text{ for } z = \{2,3\}$$

$$\frac{\mathit{dCi,1}}{\mathit{dt}} = \sum_{z=1}^{z=3} Rx_{i,4,1,z} * (\delta_j + SVR_j) - C_{i,1} * \mu_{comp}$$

$$\frac{dCi,2}{dt} = \sum_{z=1}^{z=3} Rx_{i,4,2,z} * (\delta_j + SVR_j) - C_{i,2} * \mu_{decomp}$$

$$\frac{dCli,1B}{dt} = \text{Clear*} \ \phi^* \ \epsilon^* \ \lambda_i * \text{Spi} + \text{Cl}_{i,3B} * \phi * \epsilon - \text{Cl}_{i,1B} * (\tau + \mu)$$

$$\frac{dCli,2}{dt} = \text{Clear*} \ \phi^* (1-\varepsilon) * \lambda_i * \text{Si} + \text{Cl}_{i,3} * \phi * (1-\varepsilon) - \text{Cl}_{i,2} * (\tau + \mu)$$

$$\begin{split} &\frac{dCli,2B}{dt} = \text{Clear*} \ \phi^* \ (1-\epsilon) \ ^* \lambda_i \ ^* \text{SPi} + \text{Cl}_{i,3B} \ ^* \phi \ ^* (1-\epsilon) - \text{Cl}_{i,2B} \ ^* (\tau + \mu) \\ &\frac{dCli,3}{dt} = \text{Clear*} \ \phi^* \ \epsilon \ ^* (1-\lambda_i) \ ^* \text{Si} + \text{Cl}_{i,3} \ ^* \phi - \text{Cl}_{i,3} \ ^* (\tau + \mu) \\ &\frac{dCli,3B}{dt} = \text{Clear*} \ \phi^* \ \epsilon \ ^* (1-\lambda_i) \ ^* \text{SPi} + \text{Cl}_{i,3B} \ ^* \phi - \text{Cl}_{i,3B} \ ^* (\tau + \mu) \\ &\frac{dCli,4}{dt} = \text{Clear*} \ \lambda_i \ ^* (\text{Si} + \text{SPi}) - \text{Cl}_{i,4} \ ^* (\tau + \mu) \\ &\frac{dHCC}{dt} = \chi \ ^* \sum_{j=3}^{j=4} \sum_{m=1}^{m=2} Fi, j, m + \sum_{j=3}^{j=4} \sum_{m=1}^{m=2} \sum_{z=1}^{z=3} \text{Rx}i, j, m, z + \sum_{j=3}^{j=4} \sum_{m=1}^{m=2} \sum_{z=1}^{z=3} \text{Ni}, j, m, z \end{split}$$

Force of infection

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

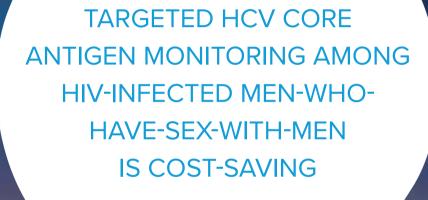
$$M$$
i, j = $\varepsilon \delta + \frac{(1-\varepsilon)CjNj}{\sum_{i=1}^{4}CiNi}$

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

$$\lambda_{i} = \lambda_{i1}^{*} (Cl_{i+j,0,m} + k_{j,m} + k_{j,4,m} + k_{j})$$

In which λ_i is the force of infection due to contact with an infected person. Similarly, λ_{ij} is the force of infection due to contact with one person that is infected with HCV and not on treatment.





Stephanie Popping, Brooke Nichols, Bart Rijnders, Jeroen van Kampen, Annelies Verbon, Charles Boucher, David van de Vijver

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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-whohave-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.¹²⁹ 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.^{51,131} 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. ^{60,61} The incidence rate of HCV among HIV-infected MSM is 0.6/100 persons-years ⁵⁸. In addition, HCV reinfections are a major concern in this population and occur in 25% - 33%. ^{51,58,71} 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. ⁷² We adapted a previously published deterministic mathematical model that represents the HCV/HIV epidemic among MSM in the Netherlands. ¹²⁶

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). 48,49,72-74,126,132 We used the estimated Dutch MSM population size, the percentage of individuals coinfected 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). 48-50,58,75,76 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). 120,133 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). 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 subdivided 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.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 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 ribayirin. 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).79

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. 83,84,128 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.⁷⁴ 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%⁹³.

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

Model Parameters of HCV transmission model among Dutch	Range/number (median)
MSM	†= calibrated
Annual HIV diagnoses among MSM per time-period	
2002-2014	720-740 ⁷³
2015	620 ⁷²
2016	580^{134}
Susceptible HIV-infected MSM in 2002	3800 t
Patients with HCV in 2002	2-10% ⁷⁶
Mortality rate HIV patients ≥350 CD4 count	1/4582*
Transmissibility of HCV	0.01-0.05 t
Clearance rate	15-25%66,67,85
Time to clearance	$40-170 \; days^{41}$
Reinfection rate	8-26.5%, per year ^{86,87}
Time from transmission until treatment	16.5 - 25 weeks ⁸⁸
Patients in stage F3, F4 in 2002	10-30% l
HCC rate	2-5% 89,90
Monitoring parameters	Diagnosed percentage
	per monitoring cycle
Biannual ALT and annual HCV antibodies	70-10083,84
HCV-PCR	90-10096,135
HCV- core antigen test	$90 \text{-} 100^{136,137}$
Treatment parameters	Range/number
SVR, DAA F0-F3	89-100% ^{6,91}
Treatment duration F0-F3	12 weeks ⁹²
SVR, DAA cirrhosis	80-95% ⁹³
Treatment duration F4 compensated and decompensated	16 weeks ⁹⁴
Re-treatment duration F0-F3	12 weeks ⁹²
Re-treatment duration F4 compensated and decompensated	16 weeks94
Quality of Life	Utility score
HIV mono-infection	0.94^{95}
Acute HCV infection	0.89 - $0.94^{88,95}$ §
HCV F0-F3 stage	$0.89 \text{-} 0.94^{95,96}$ §
Compensated cirrhosis	0.38-0.6797
Decompensated cirrhosis	0.38^{97}
Hepatocellular carcinoma	0.45^{138}
1	0.89-0.94 ^{88,95} §

Table 1. Continued

Model Parameters of HCV transmission model among Dutch MSM	Range/number (median) t = calibrated
Costs	Price in €
Doctors visit	13698
HCV RNA	105-225 [¶]
HCV core antigen	32 [¶]
Confirmation infection (PCR price)	105-225 [¶]
HCV genotyping	130-252 [¶]
Indirect laboratory cost	6.47-8
HCV genotype	130-252 [¶]
Ultrasound of the liver	90-226 [¶]
Biochemistry and liver function tests	38-46 [¶]
F3-F4 additional costs per year**	808¶
DAA regimen 12 weeks	35,000 [¶]

^{*} 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

¥ Weeks are based on the time that a patient needs to be diagnosed (16.5-25 weeks⁸⁸) 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

Abbreviations: HCV: hepatitis C virus, MSM: men having sex with men, SVR: sustained virological response, PEG-IFN: PEGylated interferon, RBV: ribavirin, DAA: direct-acting antiviral

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).96,135-¹³⁷ 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-

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

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).⁸⁸ HIV-infected MSM 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).⁹⁵ Both costs and QALY scores were discounted at 3% per year.^{100,101} 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. ⁸⁸ In addition, an HIV-infected MSM with CD4 >350 cells/µl has a life expectancy of 80 years. ⁸² Therefore, we used a 40-year time horizon to calculate the epidemiological impact and economic outcomes. ¹⁰³ 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 coinfected MSM). Several key input variables were varied: cost of DAAs ($\[\in \]$ 5,000 - $\[\in \]$ 50,000), cost of a doctor appointment (increase and decrease of 50%), spontaneous clearance rate ($\[\in \]$ 5%-30%), discounting rates ($\[\in \]$ 5%), and QALY score during DAA treatment (increase and decrease of 4%). Sensitive DAA treatment a patient will return to a QALY of 0.94,

which is similar to an individual with an HIV mono-infection.95 In addition, we changed the price of the highly sensitive diagnostic tools (€2 - €200) (HCV-PCR and HCV-cAg) and confirmatory test (HCV-PCR).

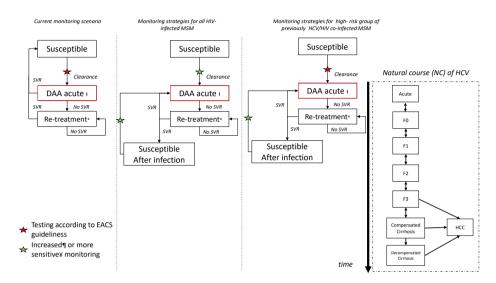


Figure 1. Simplified schematic representation of alternative monitoring strategies in the hepatitis C transmission model

This model is based on our previously published model.¹²⁶ 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 HCVantibody tests.¹²⁸ 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 HCVcAg among all HIV-infected MSM.96,135-137 In the third column the alternative monitoring strategies are targeted to the high-risk group (previously HCV/HIV co-infected MSM), while all other HIVinfected 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.

¶ Intensified monitoring from six monthly time intervals to three-monthly and monthly monitoring ¥ More sensitive monitoring using an HCV-PCR test or an HCV-core antigen test with higher probability of diagnosing HCV96,135-137

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.¹³⁹ In addition, literature suggests mixing of HCV between MSM with high-risk behaviour

regardless of HIV-status.^{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).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

over a metime nonzon				
Monitoring strategies/	Short-term HCV		HCC avoided over	
m= months of	incidence per 1000	prevalence (%)	a lifetime horizon	
monitoring interval	person-years			
Current monitoring	1.12	0.24		
ALT (m=3)	0.96	0.20	15	
ALT (m=1)	0.85	0.16	26	
HCV-core antigen (m=6)	1.08	0.23	1	
HCV-core antigen (m=3)	0.92	0.21	16	
HCV-core antigen (m=1)	0.78	0.20	26	
HCV-PCR (m=6)	1.08	0.23	1	
HCV-PCR (m=3)	0.92	0.21	16	
HCV-PCR (m=1)	0.78	0.20	26	
Targeted to the high- risk group/	Short-term HCV	Short-term HCV	HCC avoided over	
Targeted to the high- risk group/ m= months of	Short-term HCV incidence per 1000	Short-term HCV Prevalence (%)	HCC avoided over a lifetime horizon	
m= months of	incidence per 1000			
m= months of monitoring interval	incidence per 1000 person-years	Prevalence (%)	a lifetime horizon	
m= months of monitoring interval ALT (m=3)	incidence per 1000 person-years 1.01	Prevalence (%)	a lifetime horizon	
m= months of monitoring interval ALT (m=3) ALT (m=1)	incidence per 1000 person-years 1.01 0.91	0.22 0.20	a lifetime horizon 4 7	
m= months of monitoring interval ALT (m=3) ALT (m=1) HCV-core antigen (m=6)	incidence per 1000 person-years 1.01 0.91 1.08	0.22 0.20 0.23	a lifetime horizon 4 7 1	
m= months of monitoring interval ALT (m=3) ALT (m=1) HCV-core antigen (m=6) HCV-core antigen (m=3)	incidence per 1000 person-years 1.01 0.91 1.08 1.01	0.22 0.20 0.23 0.22	a lifetime horizon 4 7 1 4	
m= months of monitoring interval ALT (m=3) ALT (m=1) HCV-core antigen (m=6) HCV-core antigen (m=3) HCV-core antigen (m=1)	incidence per 1000 person-years 1.01 0.91 1.08 1.01 0.91	0.22 0.20 0.23 0.22 0.20	a lifetime horizon 4 7 1 4 7	

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

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 1.1/000 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 personyears, 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 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, $\[\epsilon 64.8 \]$ million (56.2 – 73.7), among all HIV-infected MSM. Replacing the ALT test results in higher costs of $\[\epsilon 67.1 \]$ million (58.3 – 75.0) and $\[\epsilon 92.2 \]$ 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, ϵ 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 ϵ 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 (ϵ 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 $\[mathebox{\ensuremath{\mathfrak{C}}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.

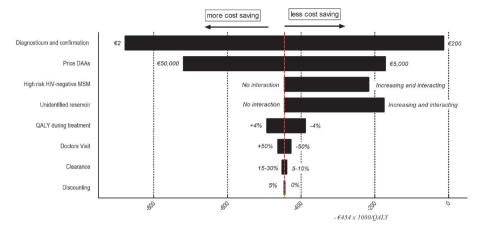


Figure 2. One-way sensitivity analysis the incremental cost-effectiveness ratio (ICERs) (€/QALY)

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

Abbreviations: DAA: direct-acting antivirals, ICER: incremental cost-effectiveness ratio, MSM menwho-have-sex-with-men.

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

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

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

Lifetime costs of the HCV	Lifetime	Incremental	Incremental	ICER (a/b) x
epidemic among HIV-infected	QALY x 1000	cost (a) € x	QALYs (b)	1000
MSM per million (€)		1000		
61.8(52.2–73.9)	357.98			
60.7(51.9–71.6)	357.99	-649	1.43	Cost-saving
63.5(54.7 –100.9)	357.99	2,900	0	Dominated*
64.8(56.2–73.7)	358.00	4,025	2.12	1,976
93.6(84.9-101.0)	358.01	27,472	2.92	9,153

^{*}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 monitoring¹²⁸

ongoing risk factors are present. However, 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 overall feeling of stigmatization and criminalization. 142,143 Yet, previously infected patients have a higher risk of reinfection.⁷¹ 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. 144 This is less likely for HIV-infected MSMs, who are integrated in HIV care, but more essential to other risk groups as HIVuninfected 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.^{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.^{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.⁴ Currently, the HCV-PCR is more costly (€105-€225) compared with the HCV-cAg test (€32), but both tests have a similar performance. ^{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. 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. ^{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. ^{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-Vizcaya et al. showed that risk-reduction in combination with an upscale of DAA treatment could result in micro-elimination. 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. ^{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. 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. 141,145,146 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. 105,141 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.^{55,56} 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 microelimination 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 (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, 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 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. 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

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

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





Stephanie Popping, Rosanne Verwijs, Lize Cuypers, Mark Claassen, Guido van den Berk, Anja De Weggheleire, Joop Arends, Anne Boerekamps, Richard Molenkamp, Marion Koopmans, Annelies Verbon, Charles Boucher, Bart Rijnders*, David van de Vijver* (*Shared authorship)

Submitted

Abstract

Introduction: In the Netherlands, unrestricted access to direct-acting antivirals (DAAs) has halved the incidence of acute hepatitis C virus (HCV) infections among HIV-infected men-who-have-sex-with-men (MSM). To develop strategies that can further reduce the spread of HCV it is important to understand the transmission dynamics of HCV. We have used phylogenetic analysis of a dense sample of MSM to provide insight into the impact of unrestricted access to DAAs on HCV transmission in the Netherlands and in Belgium.

Methods: We included 87 MSM that were recently infected with HCV genotype 1a in ten Dutch and one Belgian HIV-treatment centre. Maximum likelihood phylogenetic analysis, based on the general time reversible model, were performed on concatenated NS5A and NS5B sequences from the included MSM and from 389 highly similar control sequences that were selected from GenBank. A cluster was based on a minimum bootstrap support of 90% and a 3% genetic distance threshold.

Results: We found that 78 (90%) of individuals were part of seven major clusters. All clusters included individuals from across the study region. All clusters that were observed before the introduction of DAAs persisted after unrestricted access to DAAs became available.

Conclusion: Recently acquired HCV infections among MSM in the Netherlands and Belgium are strongly clustered and therefore highly suitable for targeted prevention strategies as contact tracing and partner notification. Importantly, despite an HCV incidence reduction after high DAA up-take and continuous monitoring, HCV transmission persisted in the same clusters.

Introduction

The World Health Organization (WHO) has set the goal to eliminate hepatitis C virus (HCV) as a global health threat by 2030. The WHO wants to achieve this ambitious goal by reducing the number of new HCV infections by 90% and by reducing HCV-related mortality by 65% in 2030.4 A key element of WHO's elimination strategy is the expansion of HCV treatment with highly curative direct-acting antivirals (DAA) and thereby preventing onward transmission to others.

A recommended strategy to reach the goals set by the WHO is by a micro-elimination approach; the local scale-up of identifying new infections and DAA treatment in welldefined populations that actively contribute to the HCV epidemic. An effort to achieve micro-elimination has been made in the Netherlands among HIV-infected men-whohave-sex-with-men (MSM) which is the predominant Dutch population in whom HCV is actively transmitted. The micro-elimination approach included HCV testing every six months followed by immediate DAA treatment in those testing positives.^{21,147} Although this effort of testing and expanded treatment access strongly reduced the number of acute infections by 50%, it was insufficient to reach micro-elimination.

Several Western European countries report high numbers of new HCV infections and reinfections among HIV co-infected MSM, driven primarily by ongoing engagement in highrisk behaviour.^{58,71,148} Moreover, more reports mention the presence of HCV among HIVnegative MSM.^{105,141,149} In addition to local transmission, HCV infections can be imported or acquired elsewhere and continue to seed the local epidemic since viruses do not respect national borders.¹⁵⁰ Therefore, a better understanding of the effect of unrestricted DAA treatment on the transmission of recently acquired HCV among MSM is needed to select appropriate future interventions and to improve micro-elimination strategies.

In this study we use phylogenetic analysis to provide further insight into HCV transmission among mostly HIV-infected MSM with a recently acquired HCV infection after the widespread use of DAA in the Netherlands and Belgium.

Methods

Study population of acutely infected HCV genotype 1a individuals

Plasma samples from MSM with recently acquired HCV genotype 1a infections who participated in two *Dutch Acute HCV in HIV studies* (DAHHS) were collected between 2013-2014 and 2016-2018. Both DAHHS studies were single-arm open-label multicentre studies investigating the efficacy of DAA therapies in mostly HIV-infected MSM with a recently acquired HCV infection.^{74,132} A detailed description of the studies and patient inclusion criteria can be found elsewhere.^{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 centres. Additionally, during the DAHHS 2 study, one Belgian HIV treatment centre (Antwerp) participated and patients from all of Belgium were referred to this centre for participation to the study. In both studies, patients were included if HCV had been diagnosed within six months after HCV infection as described elsewhere.^{74,132} All patients gave written informed consent for the use of their blood samples for research purposes.^{74,132}

The first DAHHS study started inclusions in September 2013 and lasted until December 2014. HCV genotype 1a acutely infected HIV-infected MSM (n=57) were treated with boceprevir, pegylated interferon and ribavirin for 12 weeks at a time when interferon-free treatment was yet unavailable.⁷⁴ Plasma samples were available for 45 individuals of whom 44 had been infected with HCV genotype 1a.

The DAHHS 2 study started inclusion in February 2016 ended in March 2018, when interferon-free therapy was available for the treatment of chronic HCV infections but not yet for recently acquired infections. The impact of grazoprevir and elbasvir for 8 weeks was studied among 86 MSM acutely infected with HCV, of whom 51 with a genotype 1a virus. This study also included a small number (n=4) of HIV-negative MSM. Samples from 45 individuals with a recently acquired HCV genotype 1a infection were available of which 41 from HIV-infected and 4 from HIV-negative MSM.

Viral sequencing of the non-structural proteins 5A and 5B

Two methods for sequencing were used in the two DAHHS studies: next-generation sequencing (NGS) in DAHHS 1 and Sanger population sequencing in DAHHS 2. ^{74,132} DAHHS 1 samples were sequenced by NGS on the Illumina MiSeq platform as previously published. 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 pre-filtered 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 de novo assembly of whole genomes. 151 For subsequent phylogenetic and resistance analysis only the nucleotide sequences of the NS5A and NS5B region were used. For the DAHHS 2 samples, solely the NS5A and NS5B genes were amplified by PCR and subsequently sequenced by Sanger sequencing as described before. 132

Phylogenetic analysis to evaluate transmission clustering patterns

A concatenated alignment of NS5A and NS5B sequences was assembled for 87 samples, in two samples sequencing was unsuccessful for the NS5A gene¹⁵². For each of these 87 included sequences, the 80 most highly similar HCV sequences were selected as control sequences from GenBank using BLAST (Basic Local Alignment Search Tool), 153 After removal of duplicate sequences, phylogenetic analysis was reconstructed for 389 sequences, including, 87 study samples and 302 public sequences. We included a genotype 1b sequence (EU482849) to root the phylogenetic tree within the maximum likelihood (ML) framework. The ML tree was reconstructed using a generalized time-reversible nucleotide substitution model (GTR) with 4 discrete gamma rate categories while accounting for invariable sites, as implemented within the IQTree software 154,155. Tree robustness was evaluated using 1000 ultra-fast bootstrap replicates and a Shimodaira-Hasegawa-like (SH-like) approximate likelihood ratio test (aLRT).¹⁵⁶ A cluster was defined based on a minimum ultra-fast bootstrap support of 90%, an aLRT of at least 80%, and a genetic distance threshold of 3%.¹⁵⁷ A transmission pair was defined as two sequences clustering together. The genetic distance was calculated using a Tamura and Nei model using the software MicrobeTrace. 158 Visualization of the clusters was also performed with the software MicrobeTrace. The robustness of our results was evaluated using an alignment of whole genome sequences (n=44), and subsequently compared with an alignment of concatenated NS5A and NS5B sequences (n=44) (Supplement Fig. 1).

Results

Recently acquired HCV infections in the Netherlands and Belgium are highly clustered

Phylogenetic analysis of sequences from recently acquired HCV infections showed that 78 of the 87 (90%) individuals included in the study cohort were embedded in one out of the seven identified clusters (Fig. 1 and Table 1). We identified four large clusters containing ≥10 individuals (depicted with the numbers II, III, V and VI in Table 1). (Figure 1).

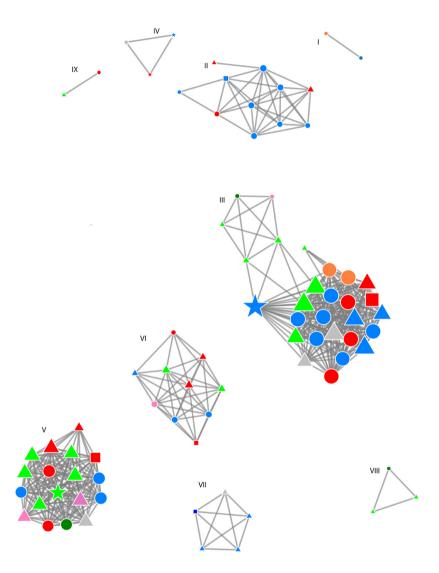


Figure 1. An overview of the clusters and transmission pairs with a genetic distance threshold <3%. The circles represent HCV infections included prior to the widespread use of DAA therapy (all in HIV-infected MSM). The triangles represent HCV infections among HIV-infected and star among HIV-negative MSM after DAA introduction. The size of the nodes represents the number of sequences to which that node was phylogenetically linked. The colours represent the centres where patients were diagnosed with HCV (dark blue= Haarlem, dark green = The Hague, grey = Arnhem, light blue = Amsterdam, light green = Antwerp (Belgium), pink = Maastricht, orange = Utrecht, red = Rotterdam). The clusters consisted only of study samples and did not include any of the control samples which mostly originated from other European countries and the United States

All clusters showed a very strong geographical variation, mostly including three different locations. Interestingly, all clusters, apart from one single cluster (number II in figure 1), included samples from one of the two major Dutch cities (Amsterdam or Rotterdam) (Figure 1).

Our study was not designed to study the HCV transmission dynamics between HIVinfected and HIV-uninfected MSM. Nevertheless, we found that the acute HCV samples of four HIV-negative MSM were embedded in clusters which also consisted of acute HCV samples from HIV-infected MSM (Figure 1). Three clusters included HIV-negative MSM (depicted with number III, IV and V in Table 1 and Figure 1) and all these individuals were sampled around the end of 2017 and originated from several different geographical locations. Interestingly, cluster IV included only 3 individuals of which 2 were HIV-negative.

Table 1. An overview of the clusters and transmission pairs obtained with maximum likelihood phylogenetic reconstruction.

Phylogenetic cluster/pair	I	II	III	IV	V	VI	VII	VIII	IX
Included 2013-2014	2	9	13	1	7	5	1	1	1
Included 2016-2018	0	2	15	2	11	5	4	2	1
Total number of MSM from our cohort	2	11	28	3	18	10	5	3	2

The samples are divided in the ones included between 2013-2014 prior to the widespread use of the direct-acting antivirals in 2015 and 2016-2018.

Clusters persist after continuously monitoring and broadened access of DAA treatment in the Netherlands

Although the widespread use of DAAs resulted in a profound reduction in the number of new HCV infections, no impact was found on the size of the phylogenetic clusters. We identified four clusters of phylogenetically linked HCV infections before the widespread introduction of DAAs in 2015 (number II, III, V, and VI in table 1 and figure 1), which were persistent after 2015. Moreover, new cluster emerged after 2015 (number IV, VII, and VIII).

Discussion

To the best of our knowledge, this is the first and largest study which describes the substantial clustering of acute HCV infections in the Netherlands and Belgium. Over 90% of the recently acquired HCV infections were embedded in one of the detected clusters. HCV infections were detected in the years preceding as well as after DAA treatment introduction, suggesting active transmission of HCV among HIV co-infected MSM. Importantly, this study showed that clusters present prior to the universal access of DAA treatment remained present, despite several elimination strategies, including compulsory notification of public health services of newly diagnosed HCV infections, partner notification and testing, annual HCV testing among HIV-infected MSM, and increased awareness amongst clinicians. Most clusters present in 2013 persisted over time and were still present up to the end of 2017 in line with recently reported data of a stabilizing HCV incidence. Our results, therefore, confirm previous model predictions which show that unrestricted DAA treatment without other prevention methods will not suffice to micro-eliminate HCV among HIV-infected MSM. 160,161

Apart from persistent clustering our study provided further insight into the transmission of recently acquired HCV infections as we identified several clusters of which four major clusters with ten or more infections. As most of the recently acquired HCV infections were embedded in large clusters, the Dutch and Belgium HCV epidemics seem highly suitable for targeted prevention strategies. Targeted prevention strategies such as, behavioural interventions and intensified HCV testing in specific risk groups followed by immediate treatment could therefore be combined to stop HCV transmission in MSM. ¹⁶⁰ The use of real-time phylogenetic analysis combined with clinical and demographic information could help to identify active transmission networks that should be targeted for public health interventions. ¹⁶²

Our data showed geographical mixing not only between both neighbouring countries but also between the different Dutch centres. However, it is possible that some of these clusters are part of larger international clusters as reported previously. ¹⁵⁰ Contrarily, a Swiss HIV cohort found most recently acquired HCV infections among HIV co-infected MSM in local clusters which is in line with our finding. ¹⁶³ As further insights into the nature of local or international transmission of new HCV infections may be beneficial to target elimination strategies, a collaboration with several large cities in Europe has been initiated to further explorer this.

In agreement with other findings, HIV-uninfected MSM diagnosed with a recently acquired HCV infection belonged to similar clusters also containing HIV-infected MSM.^{77,140,141,164} This supports a model of an HCV spill over among high-risk MSM regardless of their HIV-status. Importantly, among HIV-negative MSM, viral hepatitis screening is not standardized or regularly performed at sexual transmitted disease (STD) clinics. The actual HCV prevalence and incidence in this population is, therefore, unknown. Among HIV pre-exposure prophylaxis (PrEP) users in the in Amsterdam, there was a high baseline HCV prevalence of 4.8%, and in a similar cohort in Antwerp the baseline HCV prevalence was found to be 2.9%. ^{105,149} Although it is unclear whether these percentages can be extrapolated towards MSM with high-risk behavior, MSM PrEP users should be monitored for HCV on a regular basis. ¹⁶⁵ Moreover, prevention efforts should not be restricted to HIV status but towards risk-behaviour and thus expanded toward the high-risk HIV-negative MSM population.

This study has several limitations. Firstly, our controls were sequences submitted to GenBank, of which we know that the majority will originate from samples of chronic HCV-infected patients rather than of acutely HCV-infected patients. Moreover, sequences included in GenBank are biased towards studies from countries with resources to perform genetic sequencing. Though, we do expect ongoing HCV transmission among MSM within Europe. Most available samples consist only of an NS5B fragment, as it is typically used for genotyping purposes. However, this is a very short stretch with a much lower phylogenetic signal as compared to our concatenated alignment of the NS5A and NS5B proteins.

Secondly, the HCV epidemic in the Netherlands is predominantly driven by MSM. New HCV infections due to injection drug use have become exceptional.55,56 In several other countries, injection drug use, however, remains the major driver of the HCV epidemic. Interaction between MSM an injection drug users is uncommon. 150,166

In conclusion, we used well-defined data from the Netherlands and Belgium to unravel the transmission patterns of recently acquierd HCV infections among MSM. Our results indicated that recently acquired HCV infections among MSM in the Netherlands and Belgium are strongly clustered. This epidemic is therefore highly suitable for targeted prevention strategies such as contract tracing and partner notification followed by additional testing and treatment. Despite an HCV incidence reduction after high DAA uptake and continuously monitoring, HCV transmission continued to be present in the same clusters as beforehand. This shows that DAA therapy as standalone intervention proved to be insufficient to achieve micro-elimination; we therefore advise to implement additional prevention measurements.

Supplement

S1 – Phylogenetic comparison of whole genome sequences versus concatenated NS5A+NS5B sequences of the DAHHS 1 samples

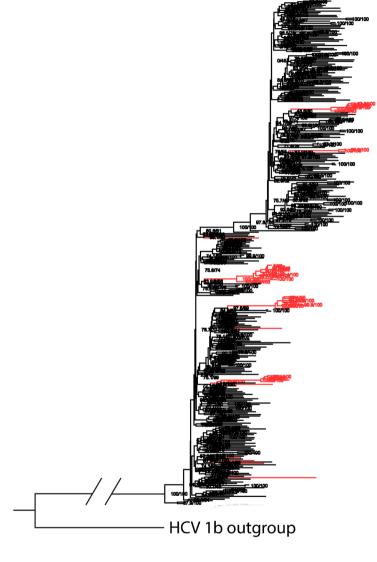


Figure 1. Upper phylogenetic tree consists of the whole genome sequences of the DAHHS 1 samples. The lower phylogenetic tree consists of the same DAHHS 1 samples only we used the concatenated NS5A+NS5B parts. Maximum likelihood analysis was performed with a GTR+G4+I model. We did not find any differences in the cluster structure and number of clusters in the tree.

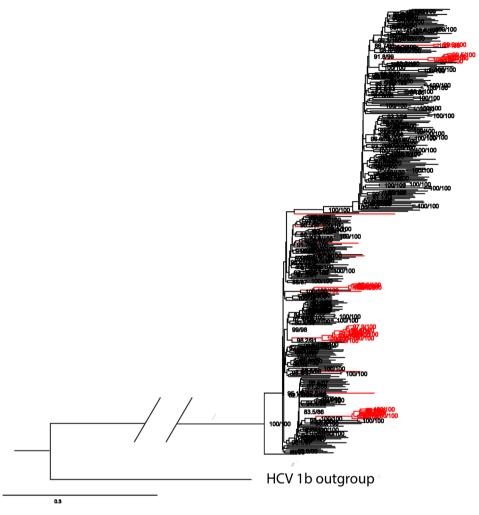
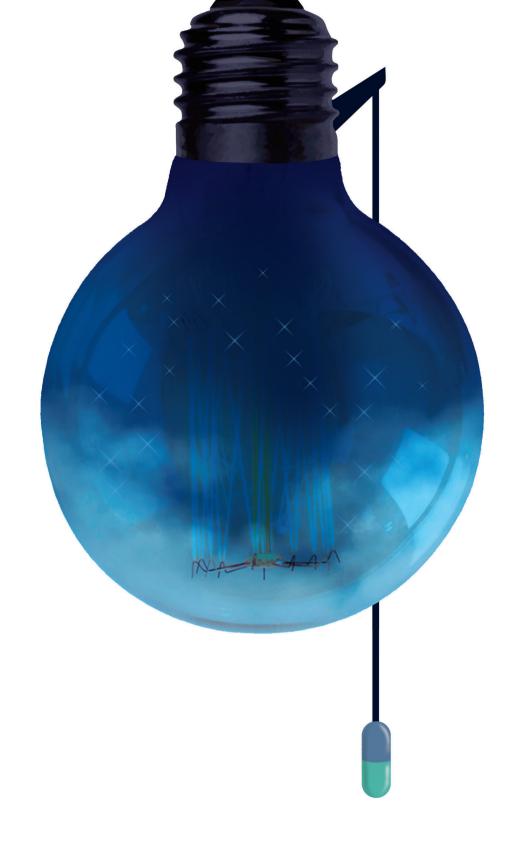
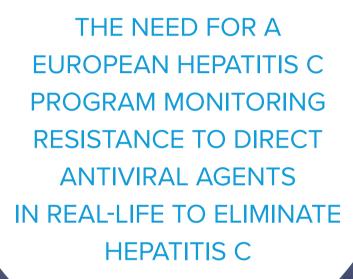


Figure 1. Continued.



Part 2



Stephanie Popping, Valeria Cento, Federico García, Francesca Ceccherini-Silberstein, Carole Seguin-Devaux⁴, David van de Vijver, Charles Boucher; on behalf of the HEPVIR working group of the European Society for translational antiviral research (ESAR)

Journal of Virus Eradication. 2018 Jul 1;4(3):179-181

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%. 167

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. 168,169 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.6 Moreover, DAAs can be used as a treatment-as-prevention tool opening the possibility for micro-elimination among subpopulations such as MSM. 161,170-172

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). 91,173-175 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 genoand 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). 176-178

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.^{3,179}

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. Start 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. 3,185 Approximately 5% (0.4% – 5.6%) of this population is treated and 4% actually cured. 185 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. 167 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.¹⁸⁶

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 retreatment 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. 189,190 Common HIV resistance databases are the Stanford HIV database (HIVDB), EuResist, and SPREAD by the European Society for Translational Antiviral Research (ESAR). 191,192

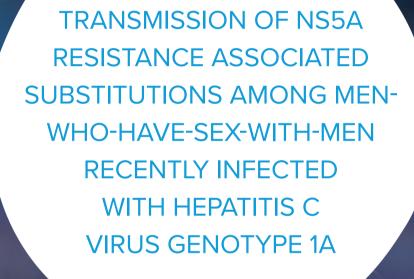
Currently, HEPCARE is the only large international collaboration within Europe combining different national surveillance programs in one central database. HEPCARE is established by ESAR, which has years of experience with HIV resistance surveillance (SPREAD program). The advantage of one central database, 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.





Stephanie. Popping, Rosanne Verwijs, Lize Cuypers, Mark Claassen, Guido van den Berk, Anja De Weggheleire, Joop Arends, Anne Boerekamps, Richard Molenkamp, Marion Koopmans, Annelies Verbon, Charles Boucher, Bart Rijnders*, David van de Vijver* - *On behalf of the DAHHS investigators*

*shared last authorship

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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 132. In both trials patients with a recently acquired HCV infection were enrolled at 11 sites in the Netherlands and Belgium^{74,132}. 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)74,132. 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 Poland¹⁹³⁻¹⁹⁵

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 (<2.5fold change)196. 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 132,196-198. 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 + elbasvir². 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 vitro¹⁹⁹.

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 France²⁰⁰. 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^{195,201,202}. 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 treated²⁰³. 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 recommended²⁰⁴. In case of significant transmission rates of clinically relevant RAS-containing viruses targeted precautions can then be taken.

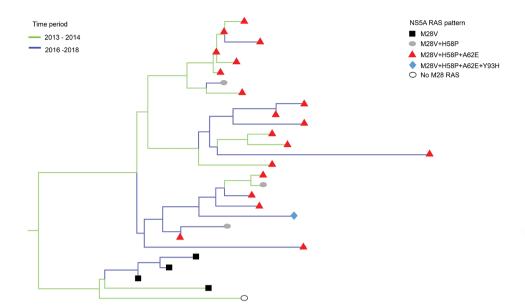


Figure 1. Phylogenetic analysis of a concatenated NS5A and NS5B alignment showed a cluster including 28 MSM (HIV-infected (n=27) and HIV-uninfected (n=1). 96% of individuals in this cluster harboured an NS5A M28V containing variant. All patients in this cluster treated with an NS5Ainhibitor (GZR/ELB 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 Hasegawaa 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 ^{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 ^{74,132}. All patients gave written informed consent for the use of their blood samples for research purposes ^{74,132}.

Sequencing

Different methods for sequencing were used in the two DAHHS studies^{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 published¹⁵¹. 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 *de novo* assembly of whole genomes¹⁵¹. 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 before¹³²

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 guidelines²⁰⁵. We used a >15% cut-off for variant calling for the sequences generated using NGS¹⁹⁴. 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 (SHlike) 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-catergory discrete gamma distribution with the software MEGA 10. A transmission pair is defined as two sequences clustering together.



Part 3





Stephanie Popping*, Lisbeth Versteegh*, Brooke Nichols, David van de Vijver, Ard van Sighem, Peter Reiss, Suzanne Geerlings, Charles Boucher, Annelies Verbon, on behalf of the ATHENA observational cohort *Equally contributing authors

Under review

Abstract

Introduction: In Europe, half of people living with HIV (PLWH) present late to care, associated with higher morbidity and mortality. This study aims to assess short- and long-term costs of HIV-care based on time of presentation and to identify other factors contributing to higher costs in the first and fifth year after antiretroviral therapy (ART) initiation.

Methods: We included ATHENA cohort data which prospectively includes 98% of PLWH in the Netherlands. PLWH who initiated ART in 2013 were included and followed over five years. PLWH were divided in three categories based on CD4 cell-count at time of ART initiation: timely presenters (CD4>350cells/ μ L), late presenters (CD4 200-350cells/ μ L or >350cells/ μ L with AIDS-defining illness) and very late presenters (CD4<200cells/ μ L). Total HIV-care cost was calculated distinguishing ART medication and non-ART medication costs (hospitalization, outpatient clinic visits, co-medications, and HIV-laboratory tests).

Results: From 1,296 PLWH, 273(21%) presented late and 179(14%) very late. Nearly half of very late presenters were of non-Dutch origin, with 21% originating from sub-Saharan Africa. The mean cost per patient in the first year was €12,902(SD€11,098), of which about two-thirds due to ART (€8,250(SD€3,142)). ART costs in the first and fifth year were comparable regardless of time of presentation. During the first year on treatment, non-ART medication costs were substantially higher among late presenters (€4,749(SD€8,009)) and very late presenters (€15,886(SD€ 21,834)), compared with timely presenters (€2,407(SD€4,511)). Higher non-ART cost was attributable to hospitalization and co-medication. The total non-ART costs incurred across five years on treatment were 56% and 246% higher for late and very late presenters respectively as compared to timely presenters.

Conclusion: Very late presentation is associated with substantial cost, with non-ART costs nearly seven times higher than for timely presenters. Hospitalization and co-medication costs are likely to continue to drive higher costs for late presenters into the future. Programs that identify patients earlier will therefore likely provide significant short- and long-term health cost savings.

Introduction

In 2018, 5.6 per 100,000 people were newly infected with HIV in the European region.²⁰⁶ Despite several diagnostic improvements and awareness campaigns, approximately half of newly diagnosed people living with HIV (PLWH) were late presenters at the time of ART initiation. 49,207,208

Late presentation, or accessing care with a CD4 cell-count <350 cells/uL or with an AIDSdefining illness, has several consequences on an individual clinical, public health, and health systems level.²⁰⁹On the individual clinical level, late presenters often experience higher morbidity and mortality.^{32,33} Patients presenting late for care often have a lower CD4-cell count and are therefore at risk for opportunistic infections and AIDS-defining malignancies, including Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancers.²¹⁰ Moreover, non-AIDS defining malignancies, cardiovascular, renal, and hepatic events appear more frequently in late presenters.^{210,211} From a public health perspective, late presenters who are mostly unaware of their infection can continue transmitting HIV to others. 212,213 Late presenters, therefore, have a large impact on epidemiological control efforts. On a health systems level, late presenters are likely to have prolonged hospitalization, extra laboratory tests, and outpatient visits.²¹⁴⁻²¹⁶ Even if there is a recovery in health, direct medical costs are estimated to remain higher over time for late presenters.217,218

The comprehensive cost of late presentation has not been assessed with a longer duration of follow-up since the World Health Organization recommended to initiate ART at CD4 cell-count <500µL.²¹⁹ We therefore assessed both the short-term (1-year) and long-term (5-year) costs over five years following ART initiation dependent on time of presentation during the natural course of HIV-infections. Furthermore, we identified the factors contributing to high short-term non-ART costs for direct HIV-care in a resource-rich setting.

Methods

In the Netherlands, HIV-care is provided by designated treatment centres As an integral part of HIV-care, the HIV Monitoring Foundation is responsible for prospectively collecting demographic data and relevant HIV and treatment data, as well as data on viral hepatitis coinfection, from PLWH in the Netherlands and receiving care in one of these treatment centres.59

This data collection is known as the ATHENA cohort which was initiated in 1998 and captures data from >98% of all patients with a diagnosed HIV-infection who are in care in the Netherlands. ²²⁰ Data collection is continuous, and the database of the ATHENA cohort is locked and updated twice a year.

At its inception, the ATHENA cohort was approved by the institutional review boards of all participating centres. Individuals can opt out after being informed by their treating physician of the purpose of data and sample collection. Data are pseudonymized and made available to investigators in a coded form. Coded data may be used for scientific purposes without further consent. For our analysis, only existing data have been used and therefore no additional review or consent was required.

At the end of 2013, 18,000 PLWH in the Netherlands were in care.⁴⁹ Men-who-have-sex-with-men (MSM) represented 71% of new diagnoses, making the Dutch HIV epidemic similar to that in other high-income countries.^{49,206} HIV-care during the study period was provided by 27 designated HIV-treatment centres.

Study design and population

We included data from PLWH from the Athena cohort who had initiated ART between 1 January 2013 and 31 December 2013 with a follow-up of five years after ART initiation (with the last data included from 31 December 2018). PLWH who enrolled the SHM database more than six months after ART initiation and individuals below the age of 18 years were excluded. PLWH were divided into three groups based on CD4 cell-count at time of ART initiation: timely presenters (CD4 cell count >350cells/ μ L), late presenters (CD4 cell-count <350 cells/ μ L or >350cells/ μ L with an AIDS-defining illness), and very late presenters (CD4 cell-count <200cells/ μ L). An AIDS-defining illness is defined according to the CDC guidelines. Any report of the occurrence of cervical cancer is considered as an AIDS-defining illness.

To describe our patient population and characterize differences between timely, late- and very-late presenters, we conducted univariate analyses using the chi-square, fisher test and unpaired t-test.

Cost analysis

The total costs of HIV-care were assessed during the first year on ART, beginning at the day of ART initiation. The total long-term costs were assessed from ART initiation and calculated over five years. All health care resources utilized during the respective periods was included. These costs included: ART medication, outpatient clinic visits, laboratory tests (viral load and CD4 cell count measurement), co-medications, and inpatient-days

(Table 1).²²¹ The quantity and type of these resources used across the respective follow-up periods was calculated. This was then multiplied by the respective unit costs. The full list of ART prices and co-medication drug prices is reported in supplement S1 and S2.²²¹

Costs are reported in 2018 Euro and presented as cost per patient per year (using means and standard deviations).

Table 1. Parameters include the non-ART costs, and cost of the most used antiretroviral regimens per day

Resources	Cost per unit (€)	Source
Price per unit (€)		
Inpatient day	679	100
Outpatient care visit	129	100
CD4 cell count	118	
HIV viral load measurement	121.5	
The mostly used first-line antiretroviral regimens n= 1344 (%)	Cost per day (€) (%)	
Tenofovir/emtricitabine/efavirenz	15.5 (29.7)	221
Tenofovir/emtricitabine/rilpivirine	23.8 (22.7)	221
Tenofovir/emtricitabine/darunavir/ritonavir	32.5 (19.3)	221
Tenofovir/emtricitabine/atazanavir/ritonavir	29.0 (7.7)	221

Hospitalization is based on the daily hospitalization price at an academic center. The outpatient care visit price is based on the midpoint of an academic and non-academic hospital outpatient visit in 2018.

Ethics

At initiation, the cohort was approved by the institutional review board of all participating centers. People entering HIV care receive written material about participation in the ATHENA cohort and are being informed by their treating physician of the purpose of collection of data, after which they can consent verbally or elect to opt-out. Data are pseudonymized before being provided to investigators and may be used for scientific purposes. A designated quality management coordinator safeguards compliance with the European General Data Protection Regulation.¹⁹

Results

In total 1529 PLWH initiated ART between 1 January 2013 and 31 December 2013. After exclusion of PLWH who enrolled the SHM database > 6 months after start of ART and adolescents (<18 years of age), a full year of follow-up was available for 1316 of PLWH (Figure 1). Of PLWH who did not have a full year of follow-up 22 PLWH died and 6 dropped-out of the SHM database. During the subsequent four years of follow-up, 28 PLWH died and 65 dropped-out of the SHM, resulting in 1223 of PLWH with five full years of follow-up.

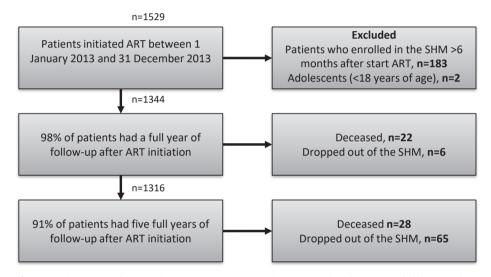


Figure 1. Flow chart of the study. 1223 PLWH remained with complete five years of follow-up data

The majority of PLWH included in our analysis were male, comparable to the overall PLWH population in the Netherlands that year.⁴⁹ The majority of the PLWH, regardless of time of presentation, were between 40 and 60 years of age. Younger PLWH (<40 years) tended to present timely in care, whereas older PLWH (>60 years) more often presented with a very late stage of HIV-infection (p<0.001).

HIV is mainly acquired through MSM (table 2). Very late presenters often acquired HIV through heterosexual contact (p<0.001). Timely presenters were mostly from Dutch origin (70%). Almost half (46%) of very late presenters were of non-Dutch origin including Sub-Saharan Africa (21%) and Central- or South America (8%) (p<0.001). PLWH who presented in HIV-care with lower CD4 cell-counts had a shorter period until ART initiation compared with those presented with CD4 cell-counts >350 cells/ μ L. Viral

suppression rates were most successful among timely presenters. Of the timely presenters 75% achieved viral suppression within 6 months after ART initiation compared with 64% and 51% in late presenters and very late presenters, respectively (p<0.001). Over half of the very late presenters switched their ART regimen during the first year of treatment compared to one-third of the timely presenters (p<0.001). Cancer mostly occurred among very late presenters in the first year after ART initiation, however, in contrast among timely presenters in the four consecutive years (p<0.001). Strikingly, of the very late presenters, more PLWH died (p<0.001) and dropped out of the Athena cohort (p<0.001) during the first year and cumulative over five years.

Resource utilization

During the first year after ART initiation very late presenters used the most healthcare resources (Table 3). The strongest differences in the first year after ART initiation was inpatient days: 0.38 (SD 2.3), 1.8 (SD 8.2), 8.3 (SD 23.7) for timely presenters, late and very late presenters, respectively. Those presenting late and very late also had slightly greater numbers of viral load counts, CD4 cell counts and outpatient visits as compared to timely presenters. Across all resource categories, with the except of ART-days, late presenters and very late presenters utilized more cumulative resources over the five-year period as compared to timely presenters.

Short-term HIV-care cost increases when presenting late in care

After the first year of ART initiation the total HIV-care cost per individual is €12,902 (SD€11,098), of which €8,250 (SD€3,142) was for ART medication and €4,652 (SD10,457) for all non-ART medication costs (Figure 2). There is a great variety of the total HIV-care cost based on the time of presentation over the course of HIV-infections mainly driven by non-ART costs (Figure 2). The non-ART costs, including co-medications, hospitalization, viral load, CD4 measurements, and outpatient visits, were an average of €2,407 (SD€4,511) per individual for timely presenters (Figure 2). For people presenting timely in care the non-ART related costs were mostly due to co-medications, €810 (SD€4,084). Non-ART costs increased remarkably to €4,749 (SD€8,009) for individuals presenting late and even more to €15,886 (SD€21,834) very late presenters (Table 4). The total non-ART costs incurred in the first year on treatment were 97% and 560% higher for late and very late presenters respectively as compared to timely presenters.

Table 2. Baseline characteristics of n=1296 PLWH who initiated ART between 1 January 2013 and 31 December 2013 (No CD4 cell-count information was available for 48 patients)

Number (%)	Non-late	Late	Very late	P-value
	presenters	presenters	presenters	
	n=844	n=273	n=179	
	Demographic ch	aracteristics		
Gender				
Male	754 (89)	240 (88)	149 (83)	0.07
Female	90 (11)	33 (12)	30 (17)	
Age				
<40	256 (30)	69 (25)	40 (22)	< 0.001
40-60	498 (59)	159 (58)	96 (54)	
>60	90 (11)	45 (16)	43 (24)	
Transmission mode				
MSM	671 (80)	185 (68)	86 (48)	< 0.001
Heterosexual	147 (17)	64 (23)	67 (37)	
Other	26 (3)	24 (9)	26 (15)	
Origin				
NL	590 (70)	183 (67)	97 (54)	< 0.001
Central/South America	73 (9)	31 (11)	14 (8)	
Northern Africa	25 (3)	9 (3)	6 (3)	
Sub-Saharan Africa	44 (5)	18 (7)	37 (21)	
Other	108 (13)	32 (12)	24 (13)	
	Clinical chara	cteristics		
Viral load				
$Suppressed \leq 6 \ months$	634 (75)	174 (64)	92 (51)	< 0.001
Cancer				
In first year on ART	18 (2)	4(1)	24 (13)	< 0.001
Following four years	59 (7)	21 (8)	6 (3)	< 0.001
Switch				
In first year on ART	281 (33)	100 (37)	101 (56)	< 0.001
Time from diagnosis to ART				
Median days [IQR]	367 [74-1123]	78 [29-832]	23 [13-55]	< 0.001

Table 2. Continued

Number (%)	Non-late presenters	Late presenters	Very late presenters	P-value		
	n=844	n=273	n=179			
Patient outcomes						
Deceased						
Year 1	4 (0.5)	3 (1)	14 (8)	< 0.001		
Cumulative at year 5	17 (2)	8 (3)	23 (13)	< 0.001		
Dropped-out						
Year 1	1 (0)	1 (0.4)	4(2)	< 0.001		
Cumulative at year 5	34 (4)	13 (5)	19 (11)	< 0.001		

Other routes of transmission included injecting drug user, transfusion (non-haemophilia related), perinatal, homo/hetero unspecified sexual contact, other including medical/dental treatment, needle accident, tattoo, piercing, circumcision, or acupuncture, and unknown. Other countries include Asia, Europe, Aruba, Belarus, Canada, Israel, Japan, Russian Federation, USA. Cancer only includes non-AIDS defining malignancies

Similar as to timely presenters non-ART costs were mostly attributed to the use of comedications. However, co-medication costs were twice the amount (€1,895 (SD€4,195)) for late presenters and ten times the amount (ϵ 8,491 (SD ϵ 10,729)) for very late presenters. Additionally, hospitalization costs are more common among late presenters (€1,256 $(SD \in 5,565)$) and very late presenters $(\in 5,644 (SD \in 16,074))$, while negligible for timely presenters (€261 (SD€1,564)) (Table 4).

Long-term HIV-care cost remain high for individuals presenting in care

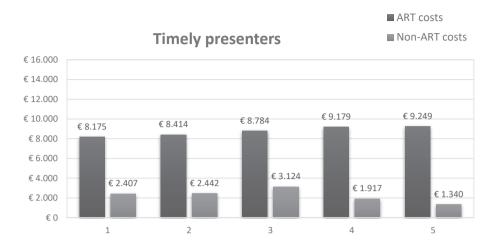
Over the years, the total annual HIV-care cost per individuals remained similar for timely presenters (range €10,289 - €11,768) (Figure 2). Although the total HIV-care cost decreased for late- and very late presenters after the first year on ART, the total HIV-care cost was 24% higher for late presenters and 19% higher for very late presenters as compared to non-late presenters at year five on ART (€12,721 and €12,221 respectively, compared with €10,289). Non-ART costs continued to drive the variation between the different patient groups, while ART costs remained stable over time (Figure 2). The long-term non-ART costs for timely presenters were an average of €1,270(SD€3,536) per individual, mostly due to co-medications (Table 4). The total non-ART costs incurred across five years on treatment were 56% and 246% higher for late and very late presenters respectively as compared to timely presenters.

Table 3. Resource utilization during the first and cumulative at five years on ART, based on presentation status

Resource utilization							
Mean (SD)	Timely presenters	Late presenters	Very late presenters				
	n=844	n=273	n=179				
First year resources used (n=1,296)							
ART days	355.6 (45.8)	359.1 (33.1)	337.8 (82.2)				
Viral loads	3.6 (1.2)	4.0 (1.4)	4.3 (1.7)				
CD4 cell count	2.7 (1.3)	3.5 (1.6)	4.0 (2.2)				
Outpatient visits	4.4 (1.9)	5.4 (2.5)	5.9 (3.2)				
Inpatient days	0.38 (2.3)	1.8 (8.2)	8.3 (23.7)				
Cumulative resources used (n=1,223)							
ART days	1821.4 (51.9)	1820.3 (63.0)	1823.2 (20.7)				
Viral loads	12.9 (3.1)	13.7 (3.6)	14.7 (3.2)				
CD4 cell count	8.0 (3.1)	9.4 (3.5)	11.0 (3.8)				
Outpatient visits	14.6 (4.6)	16.2 (5.2)	17.9 (5.8)				
Inpatient days	1.6 (9.3)	3.3 (9.3)	9.3 (25.5)				

Table 4. Non-ART costs, by component and year in HIV-care, and a comparison in costs between timely presenters and late presenters/very late presenters

	Non-ART cost divided over several cost components per						
	3	ear and ti	me of pres	entation i	n HIV-car	e	
	Year 1	Year 2	Year 3	Year 4	Year 5	Total	
Co-medication	€ 810	€ 1,188	€ 2,091	€ 1,064	€ 614	€ 5,767	
Viral loads	€ 438	€ 304	€ 297	€ 269	€ 247	€ 1,555	
CD4 cell count	€ 574	€ 355	€ 346	€ 319	€ 273	€ 1,868	
Outpatient visits	€ 261	€ 407	€ 216	€ 128	€ 87	€ 1,099	
Inpatient days	€ 324	€ 189	€ 175	€ 137	€ 117	€ 942	
Total	€ 2,407	€ 2,442	€ 3,124	€ 1,917	€ 1,340	€ 11,231	
	Late preser	nters					
Co-medication	€ 1,895	€ 793	€ 2,206	€ 2,737	€ 2,335	€ 9,966	
Viral loads	€ 487	€ 335	€ 313	€ 273	€ 240	€ 1,648	
CD4 cell count	€ 697	€ 416	€ 369	€ 320	€ 293	€ 2,094	
Outpatient visits	€ 1,256	€ 331	€ 383	€ 407	€ 358	€ 2,735	
Inpatient days	€ 414	€ 237	€ 198	€ 146	€ 121	€ 1,116	
Total	€ 4,749	€ 2,112	€ 3,470	€ 3,883	€ 3,346	€ 17,560	
Difference in cost compared to	97%	-14%	11%	103%	150%	56%	
timely presenters							
	Very late pre	senters					
Co-medication	€ 8,491	€ 4,704	€ 3,980	€ 4,951	€ 3,067	€ 25,193	
Viral loads	€ 524	€ 350	€ 320	€ 288	€ 233	€ 1,715	
CD4 cell count	€ 760	€ 447	€ 369	€ 344	€ 284	€ 2,205	
Outpatient visits	€ 5,644	€ 873	€ 776	€ 698	€ 515	€ 8,506	
Inpatient days	€ 467	€ 273	€ 211	€ 167	€ 126	€ 1,242	
Total	€ 15,886	€ 6,647	€ 5,656	€ 6,448	€ 4,224	€ 38,862	
Difference in cost compared to	560%	172%	81%	236%	215%	246%	
timely presenters							



Late presenters



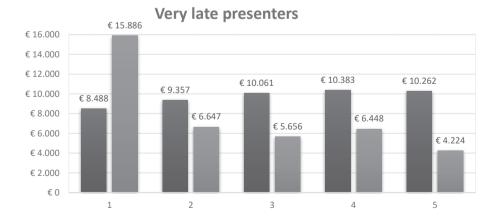


Figure 2. The mean HIV-care cost per individual divided by ART and non-ART related costs according to different stages of presentation for HIV-care

Discussion

Our results showed that apart from higher morbidity, mortality, and prolonged possibility of transmission, late presentation- and more specifically very late presentation- resulted in considerably higher short-term HIV-care costs. The higher cost per patient that initiated timeously compared to those who presented late persisted through to the end of our follow-up period at five years post ART initiation. Although the cost of ART medication comprises the greatest proportion of the total annual HIV-care costs, non-ART costs drive the increasing cost of late presenters. The short-term non-ART costs were nearly twice as high for late presenters and nearly seven-times higher for very late presenters as compared with those who presented on-time. Over a five-year period, the total HIV-care cost for late presentation were 56% higher for late presentation and 246% higher for very late presentation as compared to timely presentation.

Cost components driving the higher short-term non-ART cost among PLWH presenting late in care not surprisingly mainly included hospitalization and co-medication costs. Given the likelihood of such individuals suffering from conditions requiring frequent and prolonged hospitalization and the use of multiple co-medications. Unfortunately, after five years this increase in costs is still present mainly in the form of increased co-medication costs. This suggests that even though the clinical condition of PLWH presenting later in care improved, over time their health state remains worse than timely presenters. Similar findings were found by Krentz et al. who found higher continuing medical costs for PLWH presenting later in care related to non-ART drugs.²¹⁷

We identified several patient characteristics associated with presenting late in care such as heterosexual transmission, elderly and origin in line with other studies.^{207,208} Late presentation is often driven by postponed HIV testing due to low risk perception, lack of HIV awareness, or stigma, and can largely vary over patient groups.^{62,207,208} Especially among elderly acquiring HIV is often unconsidered due to the enduring misconception that mostly young people acquire HIV resulting in insufficient testing in this population group.^{62,222} In developed countries, however, almost half of PLWH are aged 50 or older and account for 17% of new HIV-infections. Moreover, they are more likely than younger adults to already have AIDS at the time of diagnosis. Therefore, increased awareness among both older individuals themselves and their health care providers may result in earlier case finding.

Another group which frequently present late for care and is disproportionately affected by HIV in high-income countries, concerns migrants from low- and middle-income countries. High levels of HIV-related stigma and limited access to care lead to insufficient engagement with HIV prevention and treatment services, placing migrants at risk of poor clinical outcomes.²²³ To reach the unaware population more aggressive testing could be performed by for example test individuals with conditions associated with undiagnosed HIV or implement HIV self-tests.²²⁴⁻²²⁶Additionally, increasing HIV awareness on early testing among general practitioners and other healthcare workers can be generated by organizing programs such as the Amsterdam HIV Testing Week, where large scale HIV-testing was implemented.²²⁷ This resulted in a positive response and the majority of the tested population belonged to one of the targeted risk groups, namely MSM and non-Western migrants, stressing the importance of structural free of charge low-threshold HIV-testing. Free and easy to access self-tests could also lower the barrier for stigma among several patient groups²²⁴. Furthermore, partner notification is another suitable and cost-effective strategy that may help to identify new infections in an earlier stage.²²⁸

Apart from the individual clinical benefits of timely presentation to care, our findings stress the importance of earlier identification of HIV-infection from a cost perspective in both the short and long run. Moreover, investing in earlier identification will also results in a decrease of transmission. Importantly, given that an individual presenting late incurs \$8,463 and very late incurs \$26,404 of additional costs over the first five years on treatment compared to those presenting timeously, these financial resources could be redirected to novel testing and HIV screening programmes. If a new HIV-infection could be identified for that cost, then those testing or screening programmes would quickly become cost-saving, particularly since the cost savings that we calculate here do not include the cost of onward transmission.

A major strength of our study is that the population studied can be considered to be highly representative of the PLWH and in care in the Netherlands, as more than 98 percent of those in care consent to their data being collected as part of the ATHENA cohort.²²⁰ As 91% of our study population had a five year follow-up this data provided a unique and solid opportunity to calculate the long-term economic burden of HIV-disease and the impact of presenting late for care. The distribution of mode of transmission in the Netherlands is representative of other high-income countries, making our results generalizable across the region.

Our study was the first study analyzing the long-term follow-up after ART treatment is recommended for patients with CD4 cell-counts <500 μ L²¹⁹. The guidelines of September 2015, however, changed and recommended immediately initiate ART after diagnosis of HIV. As half of our PLWH presented late in care and could therefore not benefit from the effect of early ART initiation. The effect of immediate ART initiation would, however, lower the cost of timely presenters and subsequently increasing the cost of patients presenting late and very late in care.

One of the limitations of this study is that we did not have access to all costs of HIV-care as appointments or procedures performed by a general practitioner are not included. This could result in a slight under-estimation of costs for timely presenters, since they possibly use more care provided by general practitioners. Care provided by a general practitioner is, however, less expensive than hospital care. Moreover, our resource utilization showed that timely presenters only have slightly less outpatient visits. Therefore, it would be unlikely that visits to the general practitioner office would make a substantial difference.

Secondly, we did not include cost to the patient. If considering costs from the patient perspective, those presenting very late, due to the greater number of inpatient days and outpatient visits incurred, are likely to have incurred more personal costs than those presenting on time. Including costs from the patient perspective would only have further strengthened our conclusions.

Conclusion

In conclusion, late presentation can result in substantial additional non-ART-medication costs over one- and five-year time periods. Several patient characteristics as country of origin, transmission route, and age are predictors of presenting late in care highlighting populations where aggressive testing strategies should be implemented, and awareness should be increased, to maximize both individual benefit and reduce costs. Investment in these strategies could improve clinical outcomes, prevent onward HIV transmission, and avoid these long-term excess patient costs.

Supplement

S1 Table cost of co-medication

Table S1. The cost of co-medications used in our manuscript

Tubic 51. The cos	t of co incurcations used	i iii our manascript		
ATC-code	Price (€)	ATC-code	Price (€)	
A02AA02	€ 0,16	A12AA04	€ 0,51	
A02AA04	€ 0,16	A12AX	€ 0,51	
A02AB02	€ 1,23	A14AB01	€ 21,06	
A02AD	€ 0,94	B01AA04	€ 0,08	
A02AD01	€ 1,38	B01AA07	€ 0,10	
A02BA02	€ 0,79	B01AB01	€ 25,80	
A02BA03	€ 0,76	B01AB04	€ 7,30	
A02BC01	€ 0,36	B01AB05	€ 5,80	
A02BC02	€ 2,69	B01AB06	€ 3,12	
A02BC04	€ 0,25	B01AB10	€ 10,52	
A02BC05	€ 2,90	B01AC04	€ 0,79	
A02BD04	€ 10,75	B01AC06	€ 0,58	
A03AA04	€ 0,31	B01AC07	€ 0,50	
A03BA01	€ 5,52	B01AC08	€ 0,07	
A07AA02	€ 1,50	B01AC22	€ 2,81	
A07AA08	€ 11,76	B01AC24	€ 2,49	
A07AC01	€ 10,93	B01AD04	€ 134,50	
A07DA03	€ 1,43	B01AE07	€ 3,68	
A10AB01	€ 1,12	B01AX05	€ 4,54	
A10AB05	€ 3,00	B01AX06	€ 2,81	
A10AC04	€ 5,22	B02AA02	€ 4,76	
A10AD05	€ 1,16	B02BX04	€ 832,04	
A10AE05	€ 11,33	B03AA02	€ 0,47	
A10BA02	€ 0,16	B03AA07	€ 0,09	
A10BB01	€ 0,15	B03BB01	€ 0,03	
A10BB03	€ 0,18	C01AA05	€ 0,71	
A10BB09	€ 0,14	C01BA02	€ 0,78	
A10BB12	€ 0,08	C01BC04	€ 3,86	

ATC-code	Price (€)	ATC-code	Price (€)
C02AB01	€ 0,81	C09AA05	€ 0,16
C02AC01	€ 0,70	C09AA06	€ 0,15
C02CA04	€ 0,17	C09AA09	€ 0,11
C02DC01	€ 1,76	C09BA01	€ 0,11
C03AA03	€ 0,07	C09BA02	€ 0,48
C03BA04	€ 0,10	C09BA03	€ 0,11
C03CA01	€ 0,49	C09BA04	€ 0,28
C03CA02	€ 0,57	C09CA01	€ 0,13
C03DA01	€ 0,16	C09CA03	€ 0,12
C05AA01	€ 0,09	C09CA04	€ 0,32
C05AA12	€ 0,05	C09CA06	€ 0,21
C05AE03	€ 0,04	C09CA07	€ 0,40
C05AX03	€ 0,39	C09DA01	€ 0,20
C05AX04	€ 0,08	C09DA03	€ 1,73
C05BA01	€ 0,05	C09DA04	€ 0,19
C07AA05	€ 0,38	C09DA07	€ 0,25
C07AA07	€ 14,68	C09DB01	€ 0,81
C07AB02	€ 0,92	C09DX01	€ 1,05
C07AB03	€ 0,10	C09DX04	€ 5,08
C07AB07	€ 0,42	C09XA02	€ 0,76
C07AB09	€ 73,07	C10AA01	€ 0,19
C07AB12	€ 0,26	C10AA03	€ 0,14
C07AG01	€ 4,95	C10AA04	€ 0,22
C08CA01	€ 0,06	C10AA05	€ 0,70
C08CA04	€ 17,19	C10AA07	€ 0,35
C08CA05	€ 0,34	C10AB04	€ 0,60
C08CA12	€ 0,71	C10AC01	€ 1,38
C08CA13	€ 0,13	C10AX09	€ 0,42

Table S1. Continued

Table 31. Continu	ieu				
ATC-code	Price (€)	ATC-code	Price (€)		
A10BG03	€ 0,49	C01BD01	€ 1,67		
A10BH01	€ 3,12	C01CE02	€ 17,97		
A10BX02	€ 0,61	C01DA02	€ 0,24		
A11CC	€ 0,02	C01DA08	€ 0,36		
A11CC05	€ 0,02	C01DA14	€ 0,24		
A11HA02	€ 1,02	C01EB17	€ 1,88		
D07AB02	€ 0,05	H02AB07	€ 0,11		
D07XA01	€ 0,09	H02AB08	€ 6,49		
D07XC01	€ 0,06	H02BA09	€ 0,00		
D10BA01	€ 0,69	H03AA01	€ 1,71		
G01AF02	€ 1,53	J01AA02	€ 2,20		
G02BA03	€ 0,09	J01AA08	€ 0,82		
G02BB01	€ 0,48	J01BA01	€ 0,11		
G03A	€ 0,10	J01CA04	€ 1,79		
G03AA07	€ 0,12	J01CE01	€ 9,64		
G03AA09	€ 0,09	J01CE08	€ 15,95		
G03AA13	€ 3,14	J01CF05	€ 4,73		
G03AC03	€ 1,45	J01CR02	€ 4,32		
G03AC06	€ 14,83	J01CR05	€ 11,32		
G03AC08	€ 0,11	J01DC02	€ 3,41		
G03BA03	€ 1,45	J01DD01	€ 4,97		
G03BE30	€ 0,00	J01DD04	€ 12,12		
G03CA03	€ 6,26	J01DH02	€ 17,52		
G03FB08	€ 0,23	J01EA01	€ 0,53		
G03GB02	€ 0,10	J01EC02	€ 1,39		
G03HA01	€ 2,56	J01EE01	€ 17,33		
G03HB01	€ 0,08	J01FA01	€ 8,74		
G04BD04	€ 1,38	J01FA09	€ 0,79		
G04BD07	€ 0,70	J01FA10	€ 1,41		
G04BD08	€ 0,70	J01FF01	€ 5,65		
G04BE03	€ 7,98	J01GB01	€ 22,97		

ATC-code	Price (€)	ATC-code	Price (€)
C08DA01	€ 1,35	C10BA02	€ 1,52
C08DB01	€ 0,27	D01BA02	€ 0,11
C09AA01	€ 0,10	D02AB	€ 0,04
C09AA02	€ 0,05	D04AB01	€ 0,12
C09AA03	€ 0,52	D05AX52	€ 0,34
C09AA04	€ 0,27	D06BB10	€ 0,14
J02AB02	€ 10,93	L01AA01	€ 30,64
J02AC01	€ 18,36	L01AA02	€ 2,14
J02AC02	€ 121,62	L01AA06	€ 86,39
J02AC03	€ 58,32	L01AD02	€ 7,77
J02AX01	€ 49,65	L01AX04	€ 55,05
J02AX04	€ 372,38	L01BA0	€ 582,72
J04AB02	€ 4,81	L01BA01	€ 116,36
J04AB04	€ 3,55	L01BA04	€ 875,51
J04AC01	€ 0,33	L01BC01	€ 80,78
J04AD01	€ 0,33	L01BC02	€ 18,81
J04AK01	€ 1,28	L01BC05	€ 130,91
J04AK02	€ 1,15	L01BC06	€ 115,46
J04AM02	€ 1,24	L01CA01	€ 38,15
J04BA01	€ 0,17	L01CA02	€ 16,64
J04BA02	€ 0,17	L01CA03	€ 16,64
J05AB01	€ 10,91	L01CB01	€ 38,15
J05AB04	€ 11,17	L01CB02	€ 38,15
J05AB06	€ 35,42	L01CD01	€ 736,80
J05AB11	€ 10,81	L01DB01	€ 540,81
J05AB14	€ 29,57	L01DB03	€ 193,14
J05AD01	€ 166,70	L01XA01	€ 25,89
J05AE11	€ 287,20	L01XA02	€ 115,90
J05AE12	€ 107,70	L01XC02	€ 1.117,15
J05AE14	€ 382,61	L01XE01	€ 14,32
J05AP57	€ 467,61	L01XX05	€ 10,47

Table S1. Continued

Table 31. Continued			
ATC-code	Price (€)	ATC-code	Price (€)
G04BE08	€ 8,15	J01GB03	€ 11,04
G04BE09	€ 3,51	J01MA01	€ 1,34
G04CA01	€ 0,31	J01MA02	€ 11,61
G04CA02	€ 0,22	J01MA12	€ 13,44
G04CA53	€ 1,19	J01MA14	€ 19,88
G04CB02	€ 0,38	J01XA01	€ 11,76
H02AB02	€ 4,87	J01XC01	€ 4,52
H02AB04	€ 18,57	J01XE01	€ 0,55
H02AB06	€ 6,36	J02AA01	€ 81,27
M04AC01	€ 0,51	N05BA01	€ 1,03
M05BA04	€ 0,46	N05BA05	€ 0,24
M05BA06	€ 38,18	N05BA06	€ 0,43
N01AH02	€ 2,28	N05BA12	€ 0,23
N01AH03	€ 10,91	N05CD08	€ 2,56
N01AH06	€ 13,05	N05CF01	€ 0,17
N01BB52	€ 1,37	N06AA04	€ 0,31
N01BX04	€ 302,58	N06AA09	€ 0,32
N02AA01	€ 2,17	N06AA10	€ 0,51
N02AA05	€ 3,74	N06AB03	€ 0,20
N02AB02	€ 1,02	N06AB04	€ 0,40
N02AB03	€ 19,92	N06AB05	€ 0,61
N02AC03	€ 1,85	N06AB06	€ 0,62
N02AD01	€ 8,88	N06AB08	€ 0,32
N02AE01	€ 4,68	N06AB10	€ 0,31
N02AX02	€ 0,77	N06AX05	€ 0,97
N02AX52	€ 0,77	N06AX11	€ 0,26
N02CA52	€ 1,85	N06AX12	€ 1,93
N03AB02	€ 9,31	N06AX16	€ 0,56
N03AE01	€ 0,77	N06AX21	€ 0,65
N03AF01	€ 0,85	N06BA02	€ 2,97
N03AG01	€ 1,21	N06BA04	€ 1,68

ATC-code	Price (€)	ATC-code	Price (€)
J05AX14	€ 433,11	L02BA01	€ 0,32
J05AX15	€ 379,55	L03AA02	€ 71,31
J05AX16	€ 457,86	L03AA13	€ 890,40
J05AX65	€ 481,73	L03AB1	€ 44,71
J05AX67	€ 457,86	L03AB10	€ 143,29
J05AX68	€ 272,50	L03AB11	€ 143,29
J05AX69	€ 321,61	L04AA05	€ 35,65
J06AX09	€ 83,94	L04AX01	€ 0,66
J06BA02	€ 1.258,95	M01AE02	€ 0,46
P02CA01	€ 0,69	S01EE03	€ 5,71
P02CA03	€ 3,76	V03AF03	€ 83,40
P02CF01	€ 18,37	V03AF07	€ 231,26
R01AD08	€ 1,03		
R01AD58	€ 0,32		
R03AC13	€ 1,05		
R03AK06	€ 0,80		
R03AK07	€ 1,37		
R03BA01	€ 1,06		
R03BA02	€ 0,54		
R03BA08	€ 0,53		
R03DA04	€ 0,14		
R06AD02	€ 0,49		
R06AX13	€ 0,37		
S01CA01	€ 0,21		
S01EA05	€ 0,18		
S01EB01	€ 0,84		
S01EC01	€ 0,54		
S01EC03	€ 0,30		
S01ED01	€ 3,88		
S01ED51	€ 0,41		
S01EE01	€ 2,09		

Table S1. Continued

ATC-code	Price (€)	ATC-code	Price (€)	
N03AX09	€ 15,54	N06DX02	€ 0,28	
N03AX11	€ 3,00	N07BB01	€ 0,21	
N03AX12	€ 0,92	N07BC02	€ 0,47	
N03AX14	€ 7,26	P01AB01	€ 4,99	
N03AX16	€ 2,06	P01AX06	€ 29,51	
N05AD01	€ 7,73	P01BA02	€ 0,48	
N05AG02	€ 0,37	P01BA03	€ 0,48	
N05AH02	€ 1,41	P01BB51	€ 12,56	
N05AH03	€ 0,84	P01BD01	€ 1,25	
N05AH04	€ 2,45	P01BE03	€ 16,27	
N05AX08	€ 1,01	P01CX01	€ 35,14	
N05AX12	€ 2,28	P02BA01	€ 52,35	

Costs are calculated based on the average of the lowest and highest price of the available medication and 2018 list price.²²¹ Dosage is based on an adult person of 70kg

S2 Table cost of ART

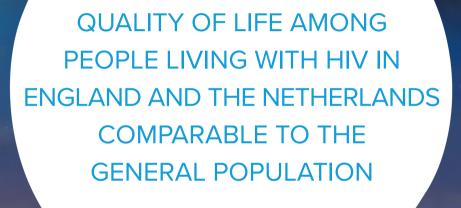
Table S2. The cost of ART as used in our manuscript

ATC-code	Price (€)	ATC-code	Price (€)
J05AE01-SQH	10.70	J05AF09	6.29
J05AE01-SQS	10.70	J05AF10	6.42
J05AE03	10.80	J05AF11	14.48
J05AE04	26.00	J05AF13	11.71
J05AE07	13.41	J05AG01	5.29
J05AE08	12.96	J05AG03	7.58
J05AE10	16.81	J05AG04	14.51
J05AF01	8.08	J05AG05	9.09
J05AF04	7.18	J05AR01	5.29
J05AF05	5.00	J05AR02	6.06
J05AF06	7.89	J05AR03	5.24
J05AF07	6.17	J05AR04	20.47
J05AF08	13.80	J05AR05	10.57

Costs are calculated based on the average of the lowest and highest price of the available medication and 2018 list price. 221

ATC-code	Price (€)	ATC-code	Price (€)
J05AR06	15.50	J05AR21	29.03
J05AR07	17.47	J05AR22	30.98
J05AR08	23.83	J05AR24	17.68
J05AR09	35.22	J05AX08	18.02
J05AR10	15.69	J05AX09	40.37
J05AR11	18.75	J05AX12	20.89
J05AR13	32.2	L01XX05	57.97
J05AR14	14.83	V03AX03	1.09
J05AR15	14.05	J05AX09	40.37
J05AR17	17.69	J05AX12	20.89
J05AR18	32.45	L01XX05	5.79
J05AR19	24.93	V03AX03	1.09
J05AR20	31.25		





Stephanie Popping^{*}, Meaghan Kall^{*}, Brooke Nichols, Evelien Stempher, Lisbeth Versteegh, David van de Vijver, Ard van Sighem, M. Versteegh, Charles Boucher, Valerie Delpech, Annelies Verbon * *Equally contributed*

Under review

Abstract

Introduction: HIV is now considered a chronic condition, and HIV-infected individuals, when treated, have a similar life expectancy as compared to the general population. Consequently, improving and ensuring a good health-related quality of life (HrQoL) among people living with HIV (PLWH) is increasingly important and has risen on the global agenda in recent years. A 'fourth 90', which includes 90% of PLWH with viral suppression have a good HrQoL, should therefore be adopted alongside the other 90-90-90 targets. This study aims to report the progress on HrQoL as the 'fourth 90' and compare against the general population in the Netherlands and England.

Methods: In the Netherlands, individuals attending the HIV outpatient clinic of a tertiary hospital were asked to complete the EQ-5D-5L from June 2016 until December 2018. In England, individuals attending one of 73 HIV outpatient clinics were randomly sampled to complete the Positive Voices survey, which included the EQ-5D-5L, from January to September 2017. HrQoL scores were combined with demographic data and compared to general population data.

Results: The EQ-5D-5L was filled-out by 895 PLWH in the NL and 4,137 in England. HrQoL $_{\rm utility}$ was 0.85 among Dutch and 0.83 among English PLWH. This equated to 98% and 94% of the general population HrQoL $_{\rm utility}$ in the Netherlands and England, respectively. Of the EQ-5D domains, anxiety/depression was mostly affected, with one-third in Dutch (35%) and almost half (47%) of English PLWH reporting symptoms. This was significantly higher compared to their respective general populations (21% NL and 31% England).

Conclusion: Overall, HrQoL_{utility} for PLWH was high in both countries and highly comparable to the general populations. Nevertheless, there should be an increased focus on anxiety and depression in the PLWH population. The EQ-5D-5L proved an easy HrQoL measurement tool and identified areas for improvement by social and behavioural interventions.

Introduction

Although new HIV-infections are preventable, significant HIV transmission continues across Europe. In 2018, approximately 140,000 people acquired HIV²²⁹. Provided that people are treated with antiretroviral therapy soon after HIV acquisition, HIV is no longer a deadly disease, but has instead transformed to a chronic, lifelong condition with a similar life expectancy as the general population.³⁸ Consequently, improving and ensuring a good health-related quality of life (HrQoL) among people living with HIV (PLWH) is increasingly important.²³⁰

HrQoL is a multidimensional construct concerned with the impact of health on an individuals' perception of their wellbeing and level of functioning in important life domains including the physical, mental, emotional, and social wellbeing. ²³¹ Over time, many validated instruments have been developed to measure HrQoL. The EuroQol 5-Dimensional 5-Level version (EQ-5D-5L) is an often used instrument which provides a health state that can be linked to the societal preferences for that specific health state, of which validity in HIV populations has been established. ²³²⁻²³⁴ Advantages of the EQ-5D-5L include its brevity, and ability to directly convert the results into a utility score for economic evaluation and comparisons. ^{235,236}

There has been a great deal of research on HrQoL among PLWH. Among virologically controlled PLWH, a substantially lower HrQoL has been reported compared to the general population. ²³⁷ However, improvements in HrQoL have been observed in PLWH due to the introduction of highly effective antiretroviral therapy (ART) with fewer side effects and earlier start of ART therapy. ²³⁸ However, much of this research has been in the context of clinical pharmaceutical trials or evaluating interventions, so the results are not generalisable to the wider population.

The importance of addressing HrQoL in people with HIV has risen on the global agenda in recent years. In 2014, UNAIDS established their 90-90-90 HIV targets, which challenges health systems to ensure that 90% of PLWH know their status, 90% of those diagnosed receive ART, and 90% of those receiving ART are virologically suppressed. This was soon followed by a paper from Lazarus et al. with a plea to acknowledge that viral suppression is not the endpoint of HIV treatment and defined a 'fourth 90' as 90 % of people with viral load suppression have good HrQoL to be adopted alongside the other 90-90-90 targets.²³⁹

In this study we aim to report the progress on HrQoL, as the 'fourth 90', and compare by gender and age group and to the general population. We defined a 'good' HrQoL in the PLWH population as achieving a utility score of at least 90% or higher of the general

population's utility score. This study uses EQ-5D-5L data from PLWH in the Netherlands and England, two high-income Western-European countries where HIV care is open-access and free at the point of access, regardless of residency status. Additionally, both countries have met the 90-90-90 targets (England in 2016 and in the Netherlands in 2017) and are therefore suitable to identify progress towards HrQoL.²⁴⁰

Methods

Study design and population

The Netherlands

A cross-sectional survey was conducted at the outpatient clinic of the Erasmus University Medical Centre (Erasmus MC), an academic tertiary hospital in Rotterdam from June 2016 to December 2018. The Erasmus MC sees over 2,000 patients annually, which is approximately 8% of all PLWH in the Netherlands. Patients attending the outpatient clinic were approached to fill-out a paper-based EQ-5D-5L. Recruitment took place from June 2016 to December 2018.

In the Netherlands, there are an estimated 23,000 PLWH, of whom around 20,000 are diagnosed and linked to care in one out of 27 HIV treatment centres.¹³⁴ PLWH have access to biannual appointments with an infectious disease specialist or nurse practitioner, which may be increased for complex cases. Of those linked to care, 93% are on treatment and of those, 95% are virologically suppressed.

England

Positive Voices is a national, cross-sectional survey of PLWH conducted by Public Health England. The survey recruited in 73 HIV outpatient clinics across England and Wales, which cumulatively represented 54,000 patients, or just over half of all PLWH in England and Wales. Patients attending a participating clinic were randomly sampled from clinic registers to fill-out an omnibus-style survey, which included the EQ-5D-5L instrument. Recruitment took place from January to September 2017.

The UK is significantly larger compared to the Netherlands, with over 180 National Health Service (NHS) centres that provide HIV treatment and care. PLWH have biannual appointments but may attend more frequently for complex cases or when newly diagnosed or starting treatment. In 2017 the UK there were approximately 101,600 PLWH of whom 92% were diagnosed²⁴¹. From the diagnosed population 98% received ART and 97% were virologically suppressed.

Data collection

The Netherlands

During the first two months of the study (June and July 2016) all individuals who visited the outpatient clinic of the Erasmus MC were approached to fill-out a paper-based EQ-5D-5L questionnaire prior to the consultation with an infectious disease specialist. Apart from Dutch the EQ-5D-5L was available in English, Spanish, French, and Portuguese. Whenever individuals refused to participate the reason for rejection was recorded.

Thereafter, the EQ-5D-5L was adopted as a suitable instrument to measure the HrQoL in PLWH \geq 18 years of age. The study was continued from July 2017 until December 2018. PLWH were asked to fill-out the EQ-5D-5L by their infectious disease specialist during their HIV consultation. The EQ-5D-5L was available in five different languages (Dutch, English, French, Spanish and Portuguese).

Data from both study phases were combined with clinical data from the "Stichting HIV Monitoring" (SHM) database (formerly known as ATHENA project).¹³⁴ The SHM collects prospective demographic, clinical, and virological data from PLWH that receive care in one of the 27 HIV treatment centres. Individuals who did not consent to have their data collected by the SHM were excluded. Additionally, duplicate questionnaires from individuals who already filled-out the EQ-5D-5L were excluded, as well as questionnaires which had incomplete data on all five dimensions or were filled-out incorrectly. Selection bias was assessed by comparing the survey population to the total PLWH population in the Netherlands (Supplement S1).¹³⁴

The study was reviewed and approved by the local Medical Ethics Committee (MEC-2016-264). Additionally, all participants were asked to sign an informed consent form and all data were anonymized.

England

Between January and September 2017, data was collected across 73 HIV clinics in England and Wales. Individuals were included if they were HIV-positive adults (aged \geq 18 years) and who could complete the survey in English. Participants were provided with several options of the response format including in clinic (paper/online), by email (online), or by mail (paper). Surveys from Welsh participants and those with incomplete data on all five dimensions or were filled out incorrectly were excluded.

The national HIV surveillance database (the HIV and AIDS Reporting System), which includes all attendances at HIV NHS specialist services and England and Wales, was used as a national sampling frame to randomly sample patients for recruitment. Pre-selected

individuals were assigned a unique six-letter survey identifier to avoid duplicate responses as well as to link the survey data to clinical and demographic data in the HIV and AIDS Reporting System.

The Positive Voices survey was designed in collaboration with PLWH, academics, clinicians, and NHS commissioners. Apart from the EQ-5D-5L this large-scale survey covers a range of socio-demographic, lifestyle, and behavioural factors including questions regarding medication, sex and relationships, and financial security.

The study was reviewed and approved by the London – Harrow Research Ethics Committee (13/LO/0279).

The EuroQol 5-Dimensional 5-Level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a validated instrument to measure HrQoL and is an updated version of the EQ-5D-3L version, with improved sensitivity and reduced ceiling effects. ²⁴² The EQ-5D-5L questionnaire contains five dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. ²³⁶ Each of these five dimensions consists of five severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Combining these domains and severity levels leads to a health state, which can be converted into a HrQoL utility score with a country-specific value set based on the valuation of the general public of the converted health state. ^{242,243} The HrQoL utility score is measured on an interval scale, where a utility score of 0 is equal to death and 1 is equal to a perfect health.

Data and statistical analysis

Patient characteristics such as gender, age, transmission mode, and country of origin were extracted from the clinical datasets. We classified transmission by mode using the following categories: men-who-have-sex-with-men (MSM), heterosexual transmission, and *other transmission routes* (including injecting drug use, haemophiliac, perinatal transmission, and unspecified modes of transmission). Country of origin was classified based on geographical region (Sub-Saharan Africa, the Middle East, South America, South-East Asia), and other high-income countries (other European countries, North America, and Oceania).

Descriptive statistics presented the distribution of responders across each of the five different domains and compared to the general population. Utility scores were calculated from the EQ-5D-5L by using the country specific value sets (Dutch and English). 243,244 We reported the mean (standard deviation) and distribution of utility scores by age and gender. Significant differences were assessed using the two-sample independent t-test, the X^2 -test, and a p-value of <0.05 was considered significant.

Comparison with the general populations

In order to compare the HrQoL of PLWH with the Dutch and English general population, previously published data from Versteegh et al. (NL) and Health Survey for England 2017 was used.^{243,245} The EQ-5D-5L utility scores and the distribution per domain of the Dutch PLWH population was compared with the Dutch general population, using the paper of Versteegh et al.²⁴³ Age- and gender-weighted utility scores of PLWH were used to match the distribution of the Dutch general population. Versteegh et al. used a stratified sampling approach for adults (>18 years of age) with age, sex, and highest educational attainment as strata, including Dutch respondents (n=979) who are representative of the Dutch general population.²⁴³ The population was 49.1% male, and the largest age category was 40-60 years old (39.5%). Most participants originated from the Netherlands (86.7%) (Supplement S2).

In order to compare the English PLWH with the English general population the EQ-5D-5L utility scores and the distributions per domain were provided on request from NHS Digital from the 2017 Health Survey for England, using the same value set.²⁴⁵ Age and gender weighted utility scores of PLWH were used to match the English general population. The 2017 Health Survey for England is an annual cross-sectional household survey of 7,136 adults (>16 years of age) representative of the English population. The population consists of 48.1% of males and the majority is aged below 40 years of age (38%) followed by 40-60 years (34%) (Supplement S2).

Results

Population in the Netherlands

During the first phase of the study, 375 individuals attending the infectious diseases outpatient clinic were considered for inclusion. A total number of 37 individuals were excluded because of HIV-2 infections, attended the outpatient clinic for a second or third time during the study period or visited for post-exposure prophylaxis. Of the 338 HIV positive people which met our inclusion criteria, 303 (89.6%) completed the EQ-5D-5L questionnaire (Figure 1). Reasons for not participating were *not feeling like filling-out a questionnaire* (6.5%), *private problems* (0.3%), *reading problems* (1.2%) and other unspecified reasons (2.4%).

During the second phase of the study 1,213 EQ-5D-5L questionnaires were filled-out. After excluding questionnaires from the second, third, or fourth visits (n=591), incorrectly complete or incomplete EQ-5D-5L (n=21) and those who did not consent to the SHM (n=9), a total of 592 questionnaires were included in the analysis. An overall total of 895 questionnaires from Phase 1 and Phase 2 remained for further analysis (figure 1).

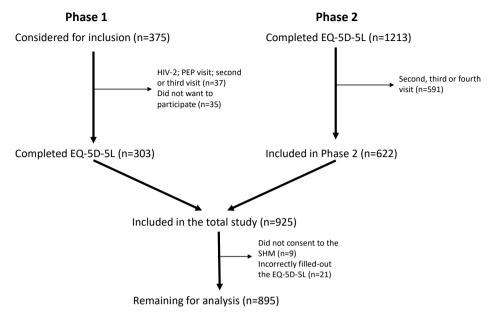


Figure 1. Flowchart representing the inclusions during the first and second phase of the study in the Netherlands. In the first phase of the study all individuals attending the infectious disease clinic were approached, after that the EQ-5D-5L was implemented in care and individuals were approach by the infectious disease specialist. The compliance in the first phase of the study was high approaching 90%.

Population in England

Overall, 4,422 people completed the survey (a 51% response rate of those who were invited to participate). This sample represents about one in twenty people living with HIV in England and Wales. Individuals who were missing data on the EQ-5D-5L (n=218) and Wales (n=67) were excluded. Since data was collected using an existing national HIV surveillance cohort as a sampling frame, the dataset provided had already been weighted to account for different probabilities of inclusion into the study at each clinic.

Baseline characteristics

In both countries most of the population was male, and significantly more males were included in the Netherlands than in England (p=0.005) (Table 1). Over half of participants were aged between 40-60 years, and of this age group there were significantly more persons included in England as compared to the Netherlands (p<0.001). Additionally, a quarter of the PLWH from both countries was below 40 years of age. The main transmission route in both countries was MSM, but significantly more MSM were included in the Netherlands than in England (p<0.001) (Table 1).

In the Netherlands almost half of the population originated from another country (47% n=421), which was comparable to England (48% n=1,922). The distribution of the regions of origin was, however, statistically significantly different between the Netherlands and England (p<0.001). In the Netherlands, the most common regions of origin included South America and Sub-Saharan Africa while in England this included Sub-Saharan Africa and other high-income countries (Europe, North America, Australia, and New Zealand) (Table 1).

Table 1. baseline characteristics of PLWH in the Netherlands and England

Baseline characteristics n (%)	PLWH	PLWH	P-value
	Netherlands	England	
	Demographic charac	teristics	
Gender			
Male	693 (77)	2945 (73)	0.005
Female	202 (23)	1100 (27)	
Age			
<40	223 (25)	904(22)	< 0.001
40-60	507 (57)	2617 (65)	
>60	165 (19)	525 (13)	
Transmission mode			
MSM	478 (60)	2165 (55)	< 0.001
Heterosexual	248 (31)	1599 (41)	
Other	69 (9)	106 (4)	
Origin			
NL/England	474 (53)	2077 (52)	< 0.001
high-income countries	77 (9)	504 (12)	
Sub-Saharan Africa	130 (15)	1120 (28)	
Middle East	19 (2)	23 (1)	
South-East Asia	40 (4)	102 (3)	
South America	155 (17)	173 (4)	

Other transmission routes included: injecting drug use (NL: 3% n=26 versus England 1% n=47), blood contact (NL: 0% n=2 versus England 0.75% n=30), perinatal (NL: 1% n=8 versus England: 0.75% n=29), and unknown routes of transmission (NL: 4% n=33 versus England: 1% n=45)

$HrQoL_{utility}$ of PLWH compared to the general population

In the Netherlands, PLWH have a mean adjusted HrQoL_{utility} score of 0.850 (± standard deviation (SD) 0.17), which is comparable to the Dutch general population at 0.869 (±SD 0.17) (Table 2). PLWH in England have a slightly lower mean adjusted HrQoL_{utility} score (0.832 \pm SD 0.23) than the general population at 0.885 (\pm SD 0.22) (p<0.001). When stratified by sex, male PLWH have slightly higher HrQoL_{utility} scores than females in both countries. However, this was also seen in the general population (table 2). In both countries, $\rm HrQoL_{utility}$ scores decreased with age both in PLWH and in the general population. In the Netherlands and England, young PLWH (< 40 years of age) had a statistically significantly lower $\rm HrQoL_{utility}$ score than the general population in the same age group (Table 2). Also middle-aged and elderly PLWH had lower utility scores that the general population, although this only reached statistical significance in England (table 2).

Using this study's definition of the 'fourth 90' of a 'good' HrQoL, which was PLWH having an $HrQoL_{utility}$ score at or above 90% of the general population $HrQoL_{utility}$ both countries met this target. In the Netherlands PLWH reached 98% and in England 94% of the utility score of the general poulation. When stratified by sex, English male PLWH scored 93% of the utility score of the male general population, which is lower than male PLWH in the Netherlands or female PLWH from both countries (Table 2).

Distribution of the five EQ-5D-5L domains

In the Netherlands, PLWH significantly reported fewer problems with mobility compared to the general population, with 21% of PLWH versus 24% of the general population reporting any mobility problems (Figure 2). In contrast, in England, PLWH had significantly more problems with mobility compared to the general population with 27% of PLWH versus 21% of the general population. Both in the Netherlands and English PLWH reported significantly more problems with self-care compared to the general population (NL: 8% PLWH vs 4% general population p<0.001; England: 13% PLWH vs 8% general population p<0.001).

The EQ-5D domain with the greatest burden of reported symptoms for PLWH was pain/discomfort, with 39% of PLWH in the Netherlands and 47% PLWH in England reporting symptoms. In the Netherlands, PLWH reported less pain/discomfort as compared to the Dutch general population, in which 49% reported problems. In contrast, PLWH in England reported more pain/discomfort than the general population, where just 43% of the population reported problems.

Remarkably, in both countries, PLWH report significantly more symptoms of anxiety/depression. Over one-third (35%) of the Dutch PLWH and almost half (47%) of PLWH in England reported anxiety/depression problems compared to one-fifth (21%) and one-third (31%) among the Dutch and English general population, respectively (p<0.001) (Figure 2).

In the Netherlands, PLWH only scored worse than the general population on two domains: self-care and anxiety/depression, which differed in England, where PLWH scored worse on all five domains. In both countries, the most striking disparity compared to the general population was for anxiety/depression.

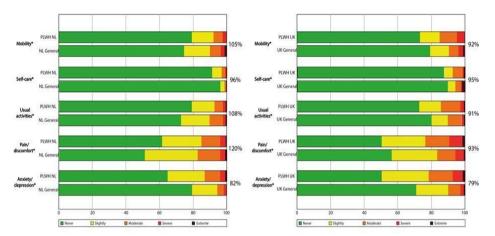


Figure 2. Comparison of the different EQ-5D-5L domains per severity level of the age and gender weighted HIV population (first bar) and the general population (second bar) in the Netherlands (left) and England (right). Raw data regarding the distribution of the Dutch general population was kindly provided by Versteegh et al. and the Health survey for England 2017^{243,245}. The percentage on the right indicates the percentage of PLWH who did not report any problems on this domain compared to the general population. *indicates a significantly difference with p<0.05.

When stratified by age, younger PLWH (<40 years of age) in both countries reported significantly more problems with anxiety/depression than older adults. Of young PLWH, 36% in the Netherlands and 47% in England reported symptoms of anxiety and depression compared to 20% and 33% among the general population (P<0.001) (Table 3). Young PLWH from England reported significantly more problems with mobility, self-care, and usual activities compared to the general population of the same age group.

In the Netherlands, middle-aged PLWH (40-60 years of age) had similar or better symptom profiles for all domains except for anxiety/depression. In contrast, in England middle-aged PLWH scored worse on all EQ-5D-5L domains compared to the general population. In both countries middle-aged PLWH scored significantly lower for anxiety/depression (Table 3).

In the Netherlands, elderly PLWH (>60 years of age) fared better for the mobility, usual activities, and pain/discomfort domains, but worse for the self-care and anxiety/depression domain. Over one-third (32%) of elderly Dutch PLWH report anxiety/depression issues compared to 15% in the Dutch general population. Additionally, 8% reported severe to extreme problems, which did not occur in the general population. In England, elderly PLWH had slightly but significantly lower scores on the domains self-care and usual activities', but much lower scores on anxiety/depression compared to the English general population. Of elderly English PLWH, 44% experienced anxiety/depression issues compared to 27% in the English general population (Table 3).

Table 2. Baseline characteristics of living with HIV in the Netherlands and England in comparison to the general populations.

	Netherlands				
	People living wi	th HIV	Gen	eral population	
Baseline	Mean utility score ±SD	90% target	n (%)	Mean utility score ±SD	
characteristics					
$HRQo_{\scriptscriptstyle LUtilit}y$	0.850 ± 0.17	98%	979(100)	0.869 ± 0.17	
Sex§					
Male	0.865 ± 0.17	98%	480(49)	0.881±0.17	
Female	0.837 ± 0.18	98%	497(51)	0.858±0.17	
Age^1					
<40	0.875±0.15*	96%	318(33)	0.906 ± 0.14	
40-60	0.851 ± 0.16	100%	388(40)	0.853 ± 0.19	
>60	0.832 ± 0.21	98%	264(27)	0.844 ± 0.17	

Raw data regarding the distribution of the Data of the Dutch general population was kindly provided by Versteegh et al. and the Health Survey for England 2017^{243,245}. Dutch and English general PLWH outcomes were age and gender weighted to match the general population. Significant difference as compared to the general population are indicated with a * for p<0.05 and ** for p<0.001. § Age weighted utility score based on the distribution of age among the general populations. 1 Gender weighted utility score based on the distribution of gender among the general populations.

England				
People living	with HIV	Genera	l population	
Mean utility score ±SD	90% target	n (%)	Mean utility score ±SD	
0.832±0.23**	94%	7,136 (100)	0.885 ± 0.22	
0.833 ± 0.23	93%	3,444 (48)	0.897 ± 0.21	
0.831 ± 0.23	95%	3,693 (52)	0.873 ± 0.20	
0.882 ±0.18**	95%	318 (33)	0.924 ± 0.16	
0.817 ±0.24**	93%	388 (40)	0.883 ± 0.22	
0.786 ± 0.24 *	94%	264 (27)	0.836 ± 0.24	

Table 3. Comparison of PLWH with the general population over EQ-5D-5L domain

Comparison of PLWH and the general population of the Netherlands

	<40 years of age		
Per EQ-5D-5L domain n(%)	People living with HIV in the Netherlands n=242	General population n=336	
Mobility			
Able to walk about	215 (89)	300 (89)	
Slight problems	21 (9)	28 (8)	
Moderate problems	4 (2)	6 (2)	
Severe problems	1 (1)	1 (0)	
Unable to walk about	0 (0)	1 (0)	
Self-care			
Able to wash or dress myself	235 (97)	330 (98)	
Slight problems	5 (2)	4(1)	
Moderate problems	2 (1)	1 (0)	
Severe problems	1 (0)	0 (0)	
Unable to walk or dress myself	0 (0)	1 (0)	
Usual activities			
Able to do usual activities	195 (81)	275 (84)	
Slight problems	36 (15)	37 (11)	
Moderate problems	8 (3)	10 (3)	
Severe problems	3 (1)	3 (1)	
Unable to do usual activities	0 (0)	1 (0)	
Pain/discomfort			
No pain	164 (68)	217 (65)	
Slight pain	53 (22)	92 (27)	
Moderate pain	21 (9)	21 (6)	
Severe pain	3 (1)	5 (2)	
Extreme Pain	1 (1)	1 (0)	
Anxiety/depression		**	
Not anxious or depressed	154 (64)	265 (79)	
Slightly	52 (22)	55 (16)	
Moderately	32 (13)	13 (4)	
Severely	3 (1)	3 (1)	
Extremely	1 (0)	0 (0)	

40 – 60 yea	40 – 60 years of age		> 60 years of age	
Dutch people living with HIV n=514	General population=379	People living with HIV in the Netherlands n=139	General population n=264	
	**			
410 (80)	265 (70)	93 (67)	158 (62)	
63 (12)	79 (21)	29 (21)	47 (18)	
30 (6)	29 (8)	9 (6)	32 (13)	
11 (2)	6 (2)	7 (5)	19 (7)	
0 (0)	0 (0)	1 (0)	0 (0)	
			*	
473 (93)	366 (97)	118 (85)	246 (93)	
21 (4)	8 (2)	14 (10)	10 (4)	
15 (3)	3 (1)	1 (1)	5 (2)	
5 (1)	0 (0)	5 (3)	0 (0)	
0 (0)	1 (0)	1 (0)	3 (1)	
	**		*	
402 (78)	257 (68)	107 (77)	180 (67)	
74 (14)	68 (18)	19 (13)	53 (20)	
26 (5)	46 (12)	8 (5)	28 (10)	
12 (2)	7 (2)	3 (2)	7 (3)	
1 (0)	1 (0)	3 (2)	0 (0)	
	**		**	
291 (57)	181 (48)	81 (59)	102 (39)	
138 (27)	120 (32)	39 (28)	98 (37)	
58 (11)	61 (16)	9 (7)	51 (19)	
27 (5)	14 (4)	5 (4)	12 (5)	
1 (0)	3 (1)	3 (2)	1 (0)	
	**		**	
333 (65)	289 (76)	94 (68)	223 (85)	
124 (24)	59 (16)	26 (19)	35 (13)	
42 (8)	21 (6)	6 (5)	6 (5)	
11 (2)	8 (2)	10 (7)	0 (0)	
4 (1)	2 (1)	2 (1)	0 (0)	

Table 3. Continued

Comparison of PLWH and the general population of England

	<40 years of age		
Per EQ-5D-5L domain n(%)	People living with HIV in England n=904	General population n=2683	
Mobility		**	
Able to walk about	803 (89)	2434 (90)	
Slight problems	50(6)	183 (7)	
Moderate problems	35(4)	52 (2)	
Severe problems	16 (2)	24 (1)	
Unable to walk about	0 (0)	9 (0)	
Self-care		**	
Able to wash or dress myself	846 (94)	2614 (97)	
Slight problems	27 (3)	54 (2)	
Moderate problems	22 (2)	27 (1)	
Severe problems	6 (1)	0 (0)	
Unable to walk or dress myself	3 (0)	0 (0)	
Usual activities		**	
Able to do usual activities	755 (84)	2406 (89)	
Slight problems	77 (9)	189 (7)	
Moderate problems	45 (5)	81 (3)	
Severe problems	22 (2)	27 (1)	
Unable to do usual activities	5 (1)	0 (0)	
Pain/discomfort			
No pain	632 (70)	1952 (73)	
Slight pain	163 (18)	508 (19)	
Moderate pain	67 (7)	161 (6)	
Severe pain	38 (4)	53 (2)	
Extreme Pain	4 (0)	27 (1)	
Anxiety/depression		**	
Not anxious or depressed	431 (48)	1791 (67)	
Slightly	266 (29)	535 (20)	
Moderately	125 (14)	267 (10)	
Severely	52 (6)	80 (3)	
Extremely	30 (3)	27 (1)	

The gender weighted levels of severity per EQ-5D-5L domains from PLWH over different age groups compared to general population of the same age group (The Netherlands = upper part and England = lower part of the table). A significantly difference of the PLWH and general population is indicated with * for a p<0.05 and ** for a p<0.001. Only England PLWH whom reported their age could be included in this analysis. Data from the general population has been kindly provided by Versteegh et al. and the Health Survey for England 243,245 .

40 – 60 years of age		> 60 years of age	
People living with HIV in England	General population=2430	People living with HIV in England	General population n=2023
n=2617	1 -1	n=525	
	*>	ŀ	
1874 (72)	1991 (81)	292 (56)	1263 (61)
278 (11)	234 (10)	96 (18)	345 (17)
325 (12)	123 (5)	93 (18)	239 (12)
130 (5)	91 (4)	42 (8)	192 (9)
10 (0)	14 (1)	2 (0)	21 (1)
	*>	•	**
2235 (85)	2282 (93)	427 (81)	1767 (86)
141 (5)	74 (3)	40 (8)	144 (7)
182 (7)	74 (3)	51 (10)	82 (4)
44 (2)	24 (1)	4(1)	41 (2)
15 (1)	0 (0)	3 (1)	21 (1)
	**	F	**
1822 (70)	2010 (81)	324 (62)	1368 (67)
325 (12)	223 (9)	85 (16)	347 (17)
309 (12)	124 (5)	80 (15)	204 (10)
126 (5)	74 (3)	28 (5)	102 (5)
35 (1)	25 (1)	8 (2)	41 (2)
	*>		
1375 (53)	1336 (55)	204 (39)	830 (40)
606 (23)	680 (28)	164 (31)	643 (31)
359 (14)	291 (12)	97 (18)	415 (20)
225 (9)	97 (4)	51 (10)	145 (7)
52 (2)	49 (2)	9 (2)	41 (2)
	*>	•	**
1314 (50)	1710 (69)	302 (58)	1492 (73)
621 (24)	446 (18)	108 (21)	368 (18)
428 (16)	198 (8)	81 (15)	143 (7)
175 (7)	74 (3)	26 (5)	41 (2)
79 (3)	28 (1)	8 (2)	21 (1)

Discussion

To the extent of our knowledge this is the largest cross-sectional study which compared the HrQoL_{utility} of PLWH in two Western European countries, the Netherlands and England, with the general population. In both countries PLWH reported a highly comparable HrQoL_{utility} as compared to the general populations. In the Netherlands, HIV positivity did not impact mobility, usual activities, and pain/discomfort, while in England all domains were affected. In both countries PLWH experienced far more anxiety/depression issues compared to HIV-uninfected individuals. Strikingly, elderly PLWH (>60 years of age) were mostly affected, with anxiety/depression issues occurring almost twice as often as in the elderly general population. PLWH from both countries exceed the 'fourth 90' for the overall HrQoL_{utility} score on HrQoL with 98% and 94% in the Netherlands and England, respectively. Nevertheless, both countries still observed a disproportionate burden of anxiety/depression among PLWH.

This study reports the progress towards the 'fourth 90', in two countries on track for the UNAIDS '90-90-90 targets'. While reaching the '90-90-90 targets' has already delivered tremendous benefits for PLWH in both countries, the 'fourth 90' is important to ensure that long and healthy lives are possible. ^{239,246} Measuring HrQoL should be considered as a standard in HIV-care given several benefits in improving care. On a clinical level, measuring HrQoL can predict survival among PLWH recieving ART and predict the occurrence of behaviour which negatively influence health status. ²⁴⁷ This practical information for clinicians can determine the involvement, adherence, self-care and subsequently prognosis of their patients. Also, prior to starting ART, HrQoL measurements could highlight aspects of a persons' health which require improvement to maximize the likelihood of a positive treatment outcome ²⁴⁸⁻²⁵⁰. On a population level, measuring HrQoL can identify areas where the health system is failing and can identify areas where needs are unmet and inform service planning and provision.

Our study demonstrated that anxiety/depression was a key issue, with up to twice as many PLWH reporting symptoms of anxiety and depression compared to the general population. Anxiety and depression were the main driver of poorer overall HRQoL_{utility} in PLWH in both the Netherlands and England. Several factors could contribute to an increase in anxiety/depression among PLWH 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. However, previous studies have shown that even compared to individuals with other chronic diseases, PLWH report significantly more anxiety/depression issues.²⁵¹ Additionally, there is an intersection of higher rates of mental health problems in marginalised population who are also at risk of HIV, such

as LGBT populations, migrants, drug users, and prisoners.²⁵² People with mental health issues or psychiatric disorders may be more likely to acquire HIV.^{253,254} Unrecognized and untreated mental health issues are associated with non-adherence and the increase of highrisk behaviour. This may facilitate HIV transmission, which can hamper the other '90-90-90 targets'.²⁴⁸⁻²⁵⁰ Therefore, it is of importance to regularly screen for anxiety/depression issues in the provision of HIV-care and, if indicated, a more in-depth assessment followed by an appropriate treatment plan, including a multidisciplinary team for PLWH with moderate to extreme anxiety/depression symptoms.⁴⁵

We found that the HrQoL utility is impacted by different factors for older and younger PLWH, indicating the changing needs of the HIV population over the life course. Young PLWH mostly struggle with anxiety/depression issues, while elderly PLWH have additional problems with self-care and usual activities. Maintaining a good HrQoL among elderly PLWH is challenging but of importance given an ageing HIV population. Older PLWH have more co-morbidities, use multiple medication, experiences more changes in physical and cognitive wellbeing, and are more prone to stressors. Additionally, age-group differences our study found country specific differences. For instance, in England middleaged PLWH experienced a significantly lower HrQoL on all domains while Dutch middleaged PLWH scored significantly better on most. This demonstrates that HrQoL is country specific and cannot be adopted from other countries. Therefore, countries should measure their own HrQoL among PLWH.

One of the major strengths of this study is that we included a large fraction of all PLWH in the Netherlands (4%) and England (5%) and that our sample isgenerally representative of the national PLWH population from both countries. Another strength of this study is the comparison of gender and age groups of PLWH with similar groups of the general population. Moreover, the Netherlands and England can provide an example to other countries as both have universal access to ART, a focus on early case finding, and solid and multidisciplinary HIV-care, which might result in a higher HrQoL than previous studies.²³⁷

Our study has several limitations. Firstly, as there is no consensus on the best definition of and measurement tool for HrQoL to assess progress towards the 'fourth 90', we defined this measure independently as a HrQoL $_{\rm utility}$ score that is 90% of the general population. This approach has several caveats, in that the interpretation is highly dependent on the validly of the EQ-5D-5L instrument to accurately measure HrQoL $_{\rm utility}$ for people living with HIV. Generic HrQoL measures such as the EQ-5D-5L, SF-36, and WHOQOL-BREF are widely used in HIV research. 233 While the EQ-5D-5L may be less sensitive to HIV-specific changes than other measurements, the EQ-5D-5L is useful due to its extensive validation, brevity, ease of administration and interpretation, the availability of several languages, and, importantly

for this study, allows comparison to the general population. Additionally, the EQ-5D-5L is frequently used and recommended among PLWH and provides responsiveness to treatment initiation, adverse events, and the development of opportunistic infections. ^{231,235,257} However, more HIV specific in-depth knowledge as, social circumstances, relationships issues, and stigmatization, should be measured with HIV-specific HrQoL instruments as for example, the WHOQOL-HIV or MOS-HIV or other patient-reported outcome measures such as stigma, social isolation, and patient engagement. ^{233,235,258} Although the EQ-5D-5L and other HrQoL instruments are very useful tools, they only measure a range of activities. Ideally, these should be offered with additional context specific measure of open-ended questions which can allow patients to expand on these modalities as well as express in their own words their lived experiences.

Secondly, England and the Netherlands have a different PLWH population and are therefore not directly comparable. From a methodological perspective, this analysis raised additional questions about the cross-country comparability of EQ-5D utility scores using different value sets and the complexity of interpreting the overall utility score. Nevertheless, this method has been performed in other studies comparing the HrQoL between different countries²⁵⁹⁻²⁶². Importantly, data showed that HrQoL between countries differ and therefore it is of importance to have country specific measurements instead of adopting values from other countries.

This study represents a first step in the process of how best to assess HrQoL in PLWH, by assembling large, existing data sources that use a standardised HrQoL measurement, and appraising the 'state of play' for HrQoL among the PLWH population in a standardised way that allows comparison to the general population. Indeed, our results identified important insights into gaps in the general health of PLWH at the population-level. However, there is a need for a standardised HrQoL measure or index to be developed, particularly considering mental health and HIV-specific issues such as stigma and ART use.

Measuring HrQoL is an important next step in HIV-care, due to the chronic nature of the disease. Our study showed that in two Western European countries, both on track for the '90-90-90 targets', the 'fourth 90' is already achieved. Although a high HrQoL utility was reported, both countries reported more anxiety/depression among the PLWH population compared to the general population, highlighting an area of health which needs more attention to improve the well-being of PLWH. Moreover, standardized HrQoL measurements implemented in daily practice can guide individualized patient care. More work is needed to identify the optimal HrQoL measure for PLWH to adopt as the 'fourth 90'.

Supplement

S1- Comparison study population with Dutch PLWH population

The Dutch PLWH population consist mostly of males, which is comparable to our study population. Nevertheless, our study population included more females (23% compared to 18% in Dutch PLWH population(p<0.001))(Table 2) (21). The major route of transmission among Dutch PLWH is through MSM, which is equal to our population (60%, p=0.429). Most Dutch PLWH are aged between 40-60 years (59%) compared to 57% in our study population (p= 0.228). Over half of the Dutch PLWH population originated from the Netherlands (57%), almost a quarter from Sub-Saharan Africa (13%) and South America (13%), and a small proportion from South-East Asia (2%). Our study population included significantly more migrants, with 17.3% originated from South America, 14.5% from Sub-Saharan Africa, and 4.5% from South East Asia (p<0.001) (Table 2). Our study population closely resembles the Dutch PLWH population, however in our study population more women and PWLH originating from other countries as the Netherlands were present.

Table 1. Comparison of the included study population with the total Dutch PLWH population.

	Study population	Dutch HIV-1 population	p-value
	(n=895) (%)	(n=25292) (%)	
Sex			< 0.001
Men	693 (77.4)	20,639 (81.6)	
Women	202 (22.6)	4,653 (18.4)	
Age			0.228
<40	223 (24.9)	4,752 (24.4)	
40-60	507 (56.6)	11,506 (59.2)	
>60	165 (18.5)	3,186 (16.4)	
Route of transmission			0.429
MSM	478 (60.1)	15,281 (60.4)	
Heterosexual	248 (31.2)	7,580 (30.0)	
Other	69 (8.7)	2,431 (9.6)	
Country of origin			< 0.001
Dutch	474 (53.0)	14,283 (56.5)	
Developed countries	77 (8.6)	1,670 (6.6)	
Sub-Saharan Africa	130 (14.5)	3,332 (13.2)	
Middle East	19 (2.1)	NA	
South-East Asia	40 (4.5)	411 (1.8)	
South America	155 (17.3)	2,949 (13.0)	

Dutch data from the "Stichting HIV Monitoring" is used²⁶³. Differences are analysed using the chisquare test. A p-value <0.05 is considered as statistically significant. Abbreviations: n=number of participants.

S2- Comparison Dutch and UK general population

Table 2. Representable general population of the Netherlands and the United Kingdom. 243,245

	The Netherlands (n=979) (%)	The UK (n=7136) (%)	P-value
Age			
<40	318 (33)	2,683 (38)	P<0.001
40-60	388 (40)	2,430 (34)	
>60	264 (27)	2,023 (28)	
Sex			
Men	480 (49)	3,444 (48)	P=0.608
Women	497 (51)	3,693 (52)	
Origin NL/UK	866 (87)	5,972 (83)	





Discussion

General discussion and future perspectives

The firm recommendation of the WHO and UNAIDS to eliminate HCV and HIV as a public health threat by 2030 requiers 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.⁵⁸ 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. 110,111 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. 112,113,264,265 Unfortunately, some countries, such as Thailand where HCV is emerging among HIV-infected MSM, still restrict DAA treatment until F2 fibrosis stage.266,267 The model from Chapter 2 calibrated to Thai epidemiological data was used to show that DAA treatment is cost-saving in Thailand.²⁶⁸ 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. 130,268 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 biannual ALT measurements. 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. 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.²⁷⁵ 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. ²⁷⁶⁻²⁷⁸ 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.⁴ 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.²⁷⁹ 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.^{280,281} 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. 12,282 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.²⁷⁵ Also for this population self-test would be a great option as it lowers the barrier to testing. 276,278 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

Population group	Recommended HCV monitoring or screening approach
HIV-infected MSM	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.
People who inject drugs	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}
Baby boomer population (USA and Canada)	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.
Prisoners	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
Sex workers	Similar approach as to HIV-infected MSM
Resource limited settings	One-step diagnostic tools such as the HCV-cAg (Chapter 3) or in more rural areas a point-of-care-test. 11,274,283,284 Screening and care should be integrated. 16,20,285

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.¹¹⁵ Moreover, this epidemic is highly suitable for contact tracing and (anonymous) partner notification.^{228,286} After implementation a follow-up, ideally with reallife phylogenetic analysis, tracking the effect of the implemented monitoring strategies should be considered.^{276,278} Next gene sequencing (NGS) is favourable over a short NS5B segment as a higher phylogenetic signal can be obtained.²⁸⁷ 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.²⁸⁸ 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.¹¹⁰ Koopsen et al. recently showed several new HCV introductions in the MSM population of Amsterdam.²⁸⁹ 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 6.²⁰⁰ 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 failures³. 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^{290,291}. 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.²⁹²

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. 132,195,293,294 Second, although newer DAAs have even higher curates there are rare occasions when treatment still fails. 295-298 Third, Chapter 6 showed the persistence of the M28V RAS over time. 299 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.³⁰⁰ 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.^{3,301,302} "Unusual" subtypes, however, have been associated with lower response rates due to various polymorphisms at relevant amino acid positions.^{300,303} More insight into theses 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".²⁹⁸ 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.^{207,304} Late presentation is associated with a high morbidity, mortality, and continuously spread of HIV.^{27,28,214,305} 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.⁶² 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.^{226,306}

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.³⁰⁷ 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 STIstandard 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.⁶² 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 STIendemic 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. 308 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.³⁰⁸

In African countries more patients present late to care than in European countries.^{27,309,310} 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.^{27,309,310} 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.311 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. 43,312,313 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'. 248-250 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. ⁴⁵ 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'.63 I agree with this as obtaining the 'fourth 90' is important to ensure that long and healthy lives are possible for PLWH. 239,246 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.^{231,235,257} 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 patientreported outcomes (PROs) could be used to determine issues on these domains.^{233,235,258} 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. 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. 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.



Hepatitis C

Natuurlijke beloop

Hepatitis C is een virale infectie die een ontsteking 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 behandeled 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 milioen mensen geïnfecteerd met HCV. Per land zijn er grote verschillen in het aantal HCV geinfecteerde 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 HIVgeïnfecteerde MSM gerelateerd aan seksuele transmissie, maar was HCV overdracht onder heteroseksuele koppels zeldzaam. Voortschrijdend inzicht toonde aan dat sub-groepen binnen HIV-geinfecteerde 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 veelvulding voorkomen van re-infecties door voortdurend risicogedrag. Behoudens Nederland komt HCV onder HIV-geïnfecteerde MSM ook veel voor in andere westerse Europese landen denk aan Engeland, Duitsland, Belgie en Frankrijk.

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 injecterende drugsgebruikers.

HIV

Natuurlijk beloop

Het humaan immunodeficiëntie virus (HIV) is een infectie die de afweercellen (CD4cellen) 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 (koortslip) 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 geimplementeerde maatregelingen om HIV te voorkomen. In de jaren 80, het begin van de HIV epidemie, 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-Westerse 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 grieperige klachten waardoor er vaak niet aan HIV wordt gedacht.

In tegenstelling tot HCV kan HIV nog niet worden genezen maar wel worden onderdrukt door een combinatie van antiretrovirale middelen (ART). Des te eerder ART wordt gestart, des te minder schade HIV heeft toegebracht aan het lichaam. Een snelle behandeling met ART heeft ook andere voordelen. Bij goed gebruik van ART zijn er geen HIV deeltjes meer in het bloed aanwezig (ondetecteerbaar) en kan HIV niet meer overgedragen worden. Dit wordt ook wel 'treatment as prevention' genoemd.

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, onddanks 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 bewerkstellingen. 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 geinfecteerden. 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 ziektelast 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 behandelings- en monitorings strategieën te bekijken waarbij naast gezondheidswinst ook gekeken wordt naar een kostenreductie. Daarnaast wordt de HCV epidemie 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 geinfecteerde mensen nog steeds laat in zorg. Naast dat late presentatie een hogere morbiditeit en mortaliteit heeft, is het ook nadeling 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 behandel 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 is 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-geinfecteerde 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 HIVgeïnfecteerde 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 resistentie. 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 barriere 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 redcutie 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.

Hoofstuk 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 komen (CD4 200-350) en 3) mensen die zeer laat in zorg komen (CD4<200). 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, polikiniek 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-geinfecteerde 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 hoofstuk 8 wordt een vergelijking gemaakt van HIV geinfecteerde mensen uit Nederland en Engeland met de ongeinfecteerde 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 bevind 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 robust 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 zieken 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

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

- 1. Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex with Men After Unrestricted Access to HCV Therapy Boerekamps A, van den Berk GE, Lauw FN, Levten EM, van Kasteren ME, van Eeden A, Posthouwer D, Claassen MA, Dofferhoff AS, Verhagen DWM, Bierman WF, Lettinga KD, Kroon FP, Delsing CE, Groeneveld PH, Soetekouw R, Peters EJ, Hullegie SJ, Popping S, van de Vijver DAMC, Boucher CA, Arends JE, Rijnders BJ. Clin Infect Dis. 2018 Apr 17;66(9):1360-1365
- 2. 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
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- 3. The need for a European hepatitis C programme monitoring resistance to direct-acting antiviral agents in real life to eliminate hepatitis C
 - Popping S, Cento V, García F, Ceccherini-Silberstein F, Seguin-Devaux C, Vijver DA, Boucher CA.
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- 5. The global campaign to eliminate HBV and HCV infection: International Viral Hepatitis Elimination Meeting and core indicators for development towards the 2030 elimination goals
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- 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

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Open Forum Infect Dis. 2019 Aug 23;6(9):ofz375. doi: 10.1093/ofid/ofz375. eCollection 2019 Sep

- 8. Targeted HCV core antigen monitoring among HIV-positive men who have sex with men is cost-saving
 - **Popping S,** Nichols B, Rijnders B, van Kampen J, Verbon A, Boucher C, van de Vijver D *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 Popping S, Verwijs NR, Cuypers L, Claassen MA, van den Berk GE, De Weggheleire A, Arends JE, Boerekamps A, Molenkamp R, Koopmans MPG, Verbon A, Boucher CAB, Rijnders BJ, van de Vijver DAMC, for the Dutch Acute HCV in HIV Study Investigators Clinical Infectious Diseases, Volume 71, Issue 8, 15 October 2020, Pages e215–e217
- 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 Popping S, Verwijs NR, Cuypers L, Claassen MAA, van den Berk GE, De Weggheleire A, Arends JE, Boerekamps A, Molenkamp R, Koopmans MPG, Verbon A, Boucher CAB, Rijnders BJ*, van de Vijver D* Manuscript submitted for publication

12. Quality of life among people living with HIV in England and the Netherland comparable to the general population

Popping S*, Kall M*, Nichols B, Stempher E, Versteegh L, van de Vijver D, van Sighem A, Versteegh M, Boucher C, Delpech V, Verbon A 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

Popping S*, Versteegh L*, Nichols B, van de Vijver D, van Sighem A, Reiss P, Geerlings S, Boucher C, Verbon A, on behalf of the ATHENA observational cohort 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 Knegt, 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 period01/11/2015 until 29/03/2020PromotorProf. dr. C.A.B Boucher

Prof. dr. A. Verbon

Education Gymnasium – Zuyderzee college Emmeloord

	Year	ECTS
In-depth courses		
Endnote	2015	0.2
Basic course on R	2016	2.0
Presenting skills for scientist	2016	1.0
Biomedical English writing course	2016	2.0
The course in Virology 2016	2016	1.0
Mathematical modelling for the control of infectious diseases - Imperial	2016	3.5
college London		
Limesurvey and Gemstracker	2017	0.5
23rd International Bioinformatics Workshop on Virus Evolution and	2018	2.0
Molecular Epidemiology – Robert Koch Institute Berlin		
Scientific Integrity	2019	0.3
BD Flow Cytometry Course	2019	0.2
Presentations		
Oral	2016	0.5
11th International Workshop on Hepatitis C – Rome	2016	0.5
Do we need surveillance for DAA resistance: how to implement it		
RIVM Modelling day	2016	0.2
Will screening reduce the epidemic of hepatitis C in HIV positive men-who-have- sex-with-men		
12th International co-infection workshop on HIV & Hepatitis - Berlin	2016	0.5
Can intensive HCV monitoring in HIV-infected MSM eliminate the epidemic		
9 th Netherlands Conference on HIV (NCHIV) – Amsterdam	2016	0.2
Intensive Hepatitis C monitoring in previously HCV infected HIV-positive MSM		
is a cost saving method to reduce the HCV epidemic		
is a cost saving memor to reduce the TIC v enthemnic		
,	2018	0.5
16th European meeting on HIV & Hepatitis- Rome The European prevalence of hepatitis C virus NS5A polymorphisms and the	2018	0.5

	Year	ECTS
AASLD - The international Liver Meeting - San Francisco	2018	0.5
Prevalence of NS3 and NS5A Resistance Associated Substitutions through		
European DAA-Failures		
European Workshop of HIV and Healthy Living - Barcelona	2019	0.5
Country specific factors determine the quality of life among people with HIV in		
two western European countries		
ARREVIR GenFor meeting, Invited speaker - Cologne	2019	0.5
CMV diagnostics in immunocompromised patients		
17th European meeting on HIV & Hepatitis - Rome	2019	0.2
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	2019	0.2
Substantial transmission of the M28V resistant associated substitution among		
acute HCV/HIV co-infected MSM		
AASLD – The Liver Meeting - Boston	2019	0.5
The Global Prevalence of Resistance Associated Substitutions (RASS) in		
"Unusual" HCV Subtypes		
The Asian Pacific Association for the Study of the Liver (APAS) - Manilla	2020	0.2
Characteristics of resistance-associated substitutions in unusual hepatitis C virus		
(HCV) subtypes		
Erasmus MC, Bridge meeting	2020	0.1
Substantial transmission of the M28V resistant associated substitution among		
acute hepatitis C HIV co-infected MSM		
Poster		
9th Netherlands Conference on HIV (NCHIV) – Amsterdam	2016	0.1
Feasibility and results of the EuroQol 5-dimension quality of life questionnaire		
among HIV-positive individuals at an outpatient clinic		
22 nd International AIDS conference - Amsterdam	2018	0.1
Late presenters drive the non-ART cost of HIV-care		
AASLD – The Liver Meeting – San Francisco	2018	0.1
The prevalence of hepatitis C virus NS5A polymorphisms in Europe		
$23^{\rm rd}$ International Bioinformatics Workshop on Virus Evolution and	2018	0.1
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)	2019	0.1
Timely emergence of letermovir resistance in a patient with primary		
immunodeficiency – the need for resistance surveillance		

ASL - International Liver conference - Vienna Genotype 4 RAS patterns in a European hepatitis C cohort 2th Netherlands Conference on HIV - Amsterdam Excellent quality of life among PLWH in the Netherlands Conference on Retroviruses and Opportunistic infections (CROI) - Boston The global prevalence of resistance associated substitutions (RAS) in "unusual HCV subtypes Conference on Retrovirusses and Opportunistic infections (CROI) - Boston Eubstantial transmission of the M28V resistant associated variant among acute tepatitis C HIV co-infected men-who-have-sex-with-men Attended conferences and symposia The Workshop on HCV therapy advances The Molecular Medicine day Elsa mini symposium Outch Annual Virology Symposium ElVM Modelling day EASL- International Liver Conference - Barcelona European workshop on HIV&Healthy living - Barcelona European workshop on HIV HIV-HEALTHY European workshop on HIV-HEALTHY European Workshop on HIV-HEALTHY Euro	Year	ECT9
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Sth International Viral Hepatitis Elimination Meeting RIVM Modelling day AREVIR-GenaFor-Meeting Verbundprojekt HIV-HEP-Master EuResist – Cologne Sth International Viral Hepatitis Elimination Meeting Feaching activities Coachen van toekomstige Erasmusartsen basis" – as part of Basis Kwalificatie Onderwijs (BKO)	2017	1.0
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Teaching activities (Coachen van toekomstige Erasmusartsen basis" – as part of Basis (Kwalificatie Onderwijs (BKO)		
Coachen van toekomstige Erasmusartsen basis" – as part of Basis Kwalificatie Onderwijs (BKO)	2019	1.0
Kwalificatie Onderwijs (BKO)		
	2016	0.1
ecture "Sexual Transmitted Infections" – Master Infection & Immunity		
J	2016	0.2
ecture "HCV resistance" – Clinical Microbiology and Virology	2016	0.2
ecture "Cost-effectiveness of HCV therapy" - Master Infection &	2016	0.2
mmunity		
Second part "Coachen van toekomstige Erasmusartsen"	2016	0.1

	Year	ECT
Lecture "Hepatitis C and different monitoring strategies" – Master	2016	0.2
Infection & Immunity		
Lecture "Chemsex" – Minor Infectious diseases (2016-2020)	annualy	0.6
Viruskenner coach	2016-2018	2.0
Lecture "Statistics" – Honours class	2018	0.2
Coaching bachelor students (7 students) in year 1, 2, and 3 of medical	2015-2019	4.0
training		
Supervision master thesis: Evelien Stempher	2019	2.0
Health-related quality of life among people living with HIV		
Infection and Immunity phylodynamics tutor	2019	0.5
Supervision honours class student: Lisbeth Versteegh	2019-2020	
Awards and travel grants		
Awards and travel grants		
2nd European workshop on HIV & Healthy Living - Young Investigator grant	2016	
American Association for the Study of Liver Diseases Foundation	2018	
2018 Early Career Investigator Award in Clinical/Translational Science		
4 th European workshop on HIV & Healthy Living - Young Investigator grant	2019	
International Liver Conference, - EASL Young Investigator Award	2019	
European meeting on HIV & Hepatitis – Young Investigator grant	2019	
Other		
ESAR meeting Rome – HepCare project introduction	2016	0.1
15th HCV DrAG meeting (HCV resistance working group)	2016	0.1
USMLE S.O.S– preparation course	2016	0.5
EuResist Medschool participant – Bioinformatics & antiviral resistance	2018	2.0
Medical Business Masterclass Roadshow	2019	1.0
E-Module – as part of "Basis Kwalificatie Onderwijs"	2020	



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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Collegas van de 16^{de} en 17^{de} bedankt voor jullie hulp waar nodig. Borrels, labuitjes, sinterkersfeesten; het was altijd dolle pret. Ik ben er trots op om deel uit te maken van de Viroscience afdeling!

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