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ORIGINAL RESEARCH

Targeted HCV core antigen monitoring among HIV-positive men who have sex with men is cost-saving

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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-positive men who have sex with men (MSM) because of their high-risk behaviour 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-positive 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 programmes.

Keywords: HIV, hepatitis C, cost-effectiveness, diagnostics, men who have sex with men, elimination

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 [1,2]. Since cured individuals cannot transmit HCV, DAAs may be used as a prevention strategy. This was shown in the Netherlands, where new HCV infections among HIV-positive men who have sex with men (MSM) were reduced by 51% after widespread DAA use in 2015 [3,4].

The World Health Organization (WHO) shares the optimism about DAAs as a prevention tool and declared the ambitious target of ending HCV as a public health threat by 2030 [5]. 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 [6]. A suitable group for micro-elimination are HIV-positive MSM since they have high-risk behaviour 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 [7].

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 [8]. Currently, guidelines advise biannual HCV-RNA or HCV-core antigen (HCV-cAg) testing among HIV-positive individuals with ongoing risk factors regardless of ALT levels [8].

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 [9–11]. 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 an HCV-PCR, which is costly [12].

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 [13]. Although both tests are more costly, more sensitive monitoring can be targeted to a very high-risk group to reduce cost [12]. Re-infections among HIV-positive MSM are common (25%–33% within 2 years after cure or clearance) and associated with ongoing risk behaviour; therefore this patient population can be defined as high-risk [11,14]. 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

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both in the HIV-positive MSM population and in a targeted high-risk HIV-positive 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 [15,16]. The incidence rate of HCV among HIV-positive MSM is 0.6/100 persons-years [4]. In addition, HCV re-infections are a major concern in this population and occur in 25%–33% [4,11,17]. The HIV epidemic is well described through a national database (ATHENA cohort), which contains anonymised clinical and demographical data of >98% of patients in HIV care in the 27 treatment centres in the Netherlands [15]. We adapted a previously published deterministic mathematical model that represents the HCV/HIV epidemic among MSM in the Netherlands [3].

Model parametrisation and calibration

We used our previously published mathematical model representing the Dutch HIV-positive 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) [3,15,18–22]. We used the estimated Dutch MSM population size, the percentage of individuals co-infected with HCV, a stable HCV incidence rate of 1.2 per 100 person-years before DAA introduction and a stable re-infection rate of 15 per 100 person-years (range 8 to 26.5 per 100 person-years) [4,19,21,23,24] (Table 1). To account for the unrestricted availability of DAAs from 2015 onwards, we validated the model's projected incidence in 2016 with the published Dutch HCV incidence data (0.4–1.0/100 person-years) [49,50]. Monte Carlo filtering techniques resulted in 132 out of 100,000 simulations that matched the Dutch HCV epidemic among HIV-positive MSM [51–53]. (Table S1).

Table 1. Model parameters and ranges used in hepatitis C virus transmission model

Model Parameters of HCV transmission model among Dutch MSM (Range/number [median], ŧ=calibrated		
Annual HIV diagnoses among MSM per time period	2002–2014 2015 2016	720–740 [18] 620 [15] 580 [25]
Susceptible HIV-positive MSM in 2002		3800ŧ
Patients with HCV in 2002		2%–10% [19]ŧ
Mortality rate HIV patients ≥350 CD4 count		1/45 [26]*
Transmissibility of HCV		0.01–0.05ŧ
Clearance rate		15%–25% [27–29]
Time to clearance		40–170 days [30]
Re-infection rate		8%–26.5%, per year [31,32]
Time from transmission until treatment		16.5–25 weeks [33]
Patients in stages F3, F4 in 2002		10%–30%ŧ
HCC rate		2%–5% [30,34]
Monitoring parameters (diagnosed per monitoring cycle [%])		
Biannual ALT and annual HCV antibodies		70–100 [9,35]
HCV-PCR		90–100 [36,37]
HCV- core antigen test		90–100 [38,39]
Treatment parameters (Range/number)		
SVR, DAA F0–F3		89%–100% [40,41]
Treatment duration F0-F3		12 weeks [42]
SVR, DAA cirrhosis		80%–95% [43]
Treatment duration F4 compensated and decompensated		16 weeks [44]
Retreatment duration F0–F3		12 weeks [42]
Retreatment duration F4 compensated and decompensated		16 weeks [44]

Quality of life (utility score)	
HIV mono-infection	0.94 [45]
Acute HCV infection	0.89–0.94 [33,45]§
HCV F0–F3 stage	0.89–0.94 [37,45]§
Compensated cirrhosis	0.38–0.67 [46]
Decompensated cirrhosis	0.38 [46]
Hepatocellular carcinoma	0.45 [47]
DAA-based therapy	0.89–0.94 [33,45]§
Costs (€)	
Doctors visit	136 [48]
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**	807.88¶
DAA regimen 12 weeks	35,000¶

HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MSM: men having sex with men; SVR: sustained virological response; PEG-IFN: pegylated interferon; RBV: ribavirin; DAA: direct-acting antiviral.

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

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

¥ Weeks are based on the time that a patient needs to be diagnosed (16.5–25 weeks [33]) with an additional number of weeks that is 'waited' until a patient reaches possible spontaneous clearance. In the model we 'wait' an additional 3-3.5 months for spontaneous 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 summarised out of different academic hospitals in the Netherlands.

Our model stratifies disease progression into individuals that spontaneously clear the virus (15%–20% of cases [27]), three stages of progressive fibrosis (METAVIR stages F0–F3) and two stages of cirrhosis (stage F4 subdivided in compensated and decompensated cirrhosis). From stage F3, F4 compensated and F4 decompensated cirrhosis patients can develop a hepatocellular carcinoma (HCC) with a rate of 2%–5%.

The rate by which HCV/HIV co-infected individuals progress from a particular stage of fibrosis to a more advanced stage of fibrosis is approximately 10% per year. This rate of progression results in a probability of having cirrhosis (stage F4) of 20.8% to 48.5% after 20 to 30 years, respectively [54] (Table S2). Due to a shortage of donors, liver transplantation has not been performed in HIV/HCV co-infected individuals in the Netherlands and is therefore not considered in the model. We assumed that during HCV treatment individuals are virologically suppressed and do not transmit HCV to others. In our model before 2012, chronically infected patients in F2–F4 fibrosis stages were treated with pegylated interferon and ribavirin. Between 2012 and 2015, boceprevir or telaprevir, in addition to pegylated interferon and ribavirin, was prescribed to chronically infected patients. We assumed that until 2015, between 67% and 75% of patients were treated for 24 weeks with pegylated interferon and ribavirin (other patients declined treatment), in agreement with the treatment guidelines that were in place. Thereafter, pegylated interferon was no longer considered since DAAs were reimbursed for all stages of HCV infection in the Netherlands.

In our model there are four different risk groups in which individuals have a different number of HIV-positive partners per year [high 20–100; medium 5–15; medium–low 1–4; low 0.1–0.9) (Table S2)] [52].

Current HCV monitoring and DAA treatment in HIV care

All HIV-positive MSM undergo HCV monitoring, using a biannual ALT test (hepatic transaminases) and an annual antibody test in which the model assumes that approximately 85% of the HCV infections are diagnosed [8,9,35]. 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 [20]. 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% [43].

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 2 weeks after HCV infection; however the HCV-cAg is less costly than the HCV-PCR [36–39] (Table 1). In addition, we intensified ALT, HCV-PCR and HCV-cAg monitoring from 6 monthly to 3 and once monthly. Since re-infection is common among HIV-positive MSM, we targeted the above-mentioned monitoring strategies

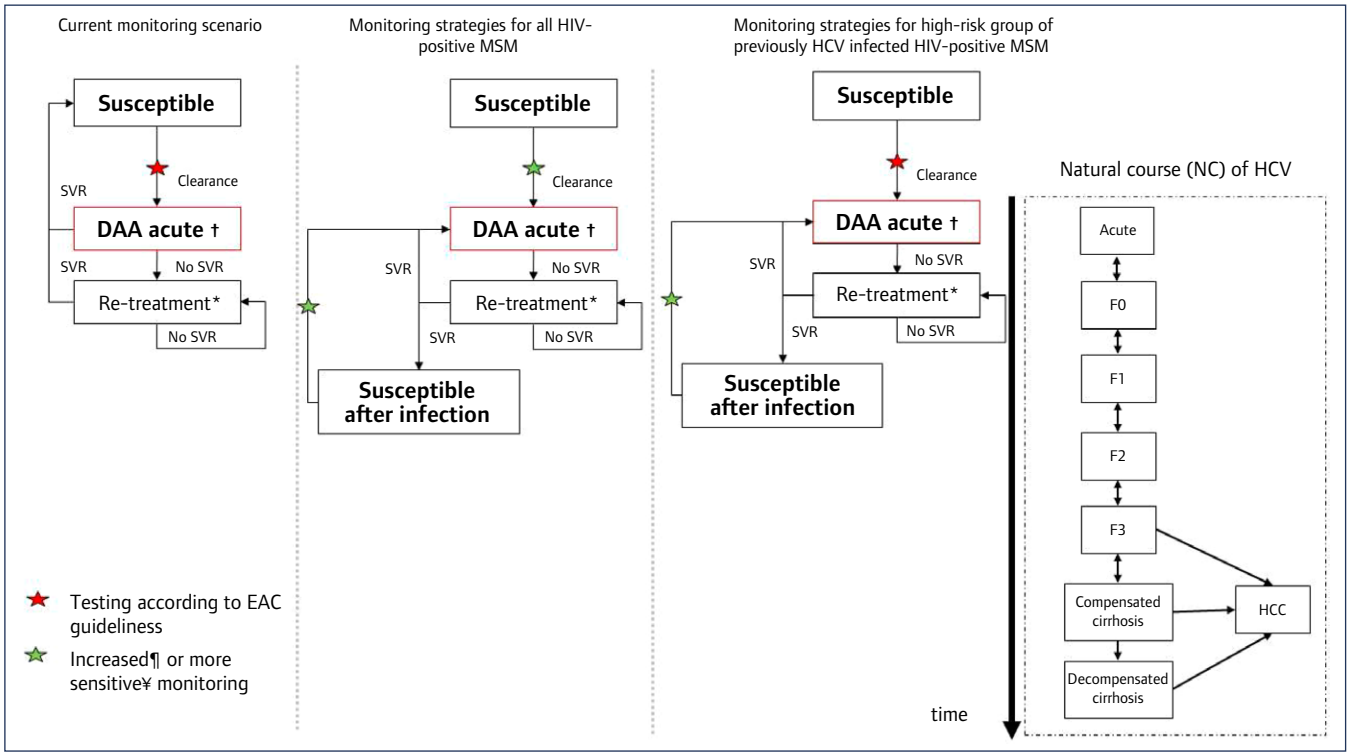

Figure 1. Simplified schematic representation of alternative monitoring strategies in the hepatitis C transmission model. This model is based on our previously published model [3]. The stage of fibrosis is represented by METAVIR stages F0, F1, F2, F3 and F4. In our model, 15%–20% of the patients can spontaneously clear their infection. The current monitoring strategy is indicated in the first column (left) and based on the European AIDS Clinical Society guidelines [8] where all patients are monitored with biannual ALT tests and annual HCV-antibody tests. In the next column, monitoring is either increased (time interval of 3-monthly or monthly) or ALT monitoring is replaced with a more sensitive test such as the HCV-PCR or HCV-cAg in all HIV-positive MSM [36–39]. In the third column the alternative monitoring strategies are targeted to the high-risk group (previously HCV-infected HIV-positive MSM), while all other HIV-positive 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. DAA: direct-acting antivirals; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MSM: men who have sex with men; SVR: sustained virological response. ¶ Intensified monitoring from 6-monthly time intervals to 3-monthly and monthly monitoring. ¥ More sensitive monitoring using an HCV-PCR test or an HCV-core antigen test with higher probability of diagnosing HCV [36–39]

solely to a group of previously HCV-infected HIV-positive 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-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 shortened since DAA treatment is started immediately after diagnosis, for example, within 3 or 1 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 hepatocellular carcinomas avoided, are evaluated among HIV-positive 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 Centers 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) [33]. HIV mono-infected MSM have a QALY of 0.94 [45]. 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 [45]). Both costs and QALY scores were discounted at 3% per year [55,56]. For this study, we used a willingness-to-pay threshold of €20,000 per QALY.

HIV-positive MSM are co-infected with HCV at a median age of 40 years [33]. In addition, an HIV-positive MSM with CD4 >350 cells/μL has a life expectancy of 80 years [26]. Therefore, we used a 40-year time horizon to calculate the epidemiological impact and economic outcomes [57]. 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-infected HIV-positive MSM). Several key input variables were varied: cost of DAAs (€5000–€50,000), cost of a doctor appointment (increase and decrease of 50%), spontaneous clearance rate (5%–30%), discounting rates (0%–5%) and QALY score during DAA treatment (increase and decrease of 4%) [33,45]. After DAA treatment a patient will return to a QALY of 0.94, which is the same value as an individual with an HIV mono-infection [45]. In addition, we changed the price of the highly sensitive diagnostic tools (€2–€200) (HCV-PCR and HCV-cAg) and confirmatory test (HCV-PCR).

Recently, the HCV prevalence has been increasing among HIV pre-exposure prophylaxis (PrEP) users, in contrast to a stabilising prevalence among HIV-negative MSM [58]. In addition, the literature suggests mixing of HCV among MSM with high-risk behaviour regardless of HIV status [59–61]. 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) [62]. In addition, we accounted for the impact of continuing transmission and interaction with undiagnosed HCV-infected individuals, such as HIV-negative MSM, HIV-positive 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-positive MSM.

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-positive MSM

Intensifying ALT monitoring with 3-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 the incidence rate to 0.9/1000 person-years, with a 0.16% prevalence (Table 2). When ALT monitoring is replaced by a simplified monitoring strategy based on the HCV-PCR or HCV-cAg test, our model demonstrates that 6-monthly monitoring results in an incidence rate of 1.1/000 person-years and a 0.23% prevalence. With intensified HCV-PCR or HCV-cAg monitoring, similarly as seen with ALT monitoring: the incidence rate declines to 0.9/1000 person-years, with a 0.19% prevalence (20% reduction) with 3-monthly intervals, and to 0.8/1000 person-years, with a 0.16% prevalence (33% reduction) with monthly intervals. 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-infected HIV-positive MSM

Intensifying ALT monitoring with time intervals of every 3 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-infected HIV-positive 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 of 1.1/1000 person-years (Table 2), with a 0.23 % prevalence. With intensified monitoring, the incidence rate declines to 1.0/1000 person-years, with a 0.22% prevalence (8% reduction), and to 0.9/1000 person-years, with a 0.20% prevalence (17% reduction), when monitoring with 3-monthly and monthly time intervals regardless of test, respectively. Intensified and simplified monitoring results in a maximum of seven 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-positive MSM over a lifetime horizon (Table 3). When monitoring with ALT is increased to 3-monthly time intervals, a more costly scenario results, that is, €64.8 million (56.2–73.7), among all HIV-infected MSM. Replacing the ALT test results in higher costs of €67.1 million (58.3–75.0) and €92.2 million

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

Monitoring strategies (m=months of monitoring interval)	Short-term HCV incidence per 1000 person-years	Short-term HCV prevalence (%)	HCC avoided over a lifetime horizon
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/ m=months of monitoring interval	**Short-term HCV incidence per 1000 person years**	**Short-term HCV prevalence (%)**	**HCC avoided over a lifetime horizon**
ALT (m=3)	1.01	0.22	4
ALT (m=1)	0.91	0.20	7
HCV-core antigen(m=6)	1.08	0.23	1
HCV-core antigen (m=3)	1.01	0.22	4
HCV-core antigen (m=1)	0.91	0.20	7
HCV-PCR (m=6)	1.08	0.23	1
HCV-PCR (m=3)	1.01	0.22	4
HCV-PCR (m=1)	0.91	0.20	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 6-monthly time intervals to 3- and monthly time intervals.
ALT: alanine aminotransferase; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; PCR: polymerase chain reaction.

(82.2–100.6) when monitored every 3 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 S4).

A more targeted monitoring approach towards the high-risk group (previously HCV-infected HIV-positive MSM) using the HCV-cAg, however, was less costly at €60.7 million (51.9–71.6) for the total HCV epidemic among HIV-positive MSM (Table 3). Monitoring with the HCV-PCR, as recommended by the European AIDS Clinical Society guidelines for individuals with ongoing risk behaviour, was slightly more expensive at €63.5 million (56.2–73.7). Monitoring with both the HCV-cAg and HCV-PCR test results in an increase of 1.4 QALYs over 40 years, compared with the current monitoring approach. Since the HCV-cAg is less costly and results in an increase in QALYs, this strategy is considered cost-saving. Since the HCV-PCR is more costly (€63.5 million) and results in a similar number of QALYs gained (1.4), this is less favourable and considered dominated. All other monitoring interventions cost more and result in a similar number of QALYs; therefore, they are either not cost-effective or dominated (Table 3, Table S4).

Sensitivity analysis

We performed a one-way sensitivity analysis to identify the factors that most strongly influence the cost-effectiveness ratio (Figure 2). Our results show that the incremental cost-effectiveness ratio (ICER) strongly depends on the price of the diagnostic and confirmation tool, whereas a decrease results 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 €5000. 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 such as QALYs, cost of a doctor visit, clearance and discounting had a limited impact on the cost-effectiveness ratios.

Discussion

We used mathematical modelling to compare the impact of alternative HCV monitoring strategies on the HCV epidemic among HIV-positive MSM in the Netherlands. Alternative monitoring strategies, that is, intensified ALT monitoring or monitoring with a 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-infected HIV-positive 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-infected HIV-positive MSM with the hypothesis of a higher risk of HCV infection due to high-risk behaviour (re-infection rates are 25%–33%) [11,14]. 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 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

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 with S1 at 20 years	Prevalence reduction (%) at 20 years	Cumulative HCCs avoided over 40 years	Lifetime costs of the HCV epidemic among HIV-positive MSM per million (€)	Lifetime QALY×1000	Incremental cost (*a*) €×1000	Incremental QALYs (*b*)	ICER (*a*/*b*)×1000
Current monitoring strategy (S1)				61.8 (52.2–73.9)	357.98			
HCV core antigen (m=6) high-risk group	19	2.8	1	60.7 (51.9–71.6)	357.99	–649	1.43	Cost-saving
HCV PCR (m=6) High-risk group	19	2.8	1	63.5 (54.7–100.9)	357.99	2900	0	Dominated*
ALT (m=3) high-risk group	57	7.9	4	64.8 (56.2–73.7)	358.00	4025	2.12	1976
HCV-core antigen (m=1) high-risk group	124	15.5	7	93.6 (84.9–101.0)	358.01	27,472	2.92	9153

Table shows the short-term epidemiological impact, long-term sequelae (cumulative avoided HCCs) and cost-effectiveness over a lifetime horizon of 40 years. The 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 considered to be dominated. Costs and QALYs are calculated over a lifetime horizon of 40 years. A willingness-to-pay threshold of €20,000 is considered. The following monitoring strategies are dominated: ALT monitoring (3-monthly and monthly) among all HIV-positive MSM and HCV-PCR and HCV-cAg monitoring among all HIV-infected MSM (6-monthly, 3-monthly, and monthly). For the full figure, see supplement (Table S4).
ICER: incremental cost-effectiveness ratio; HCC: hepatocellular carcinoma; HCV: hepatitis C; HCV-cAg: HCV-core antigen; S1: current monitoring approach based on ALT monitoring [8].
* When the compared strategy has equal or less QALYs compared with the previous less costly scenario.

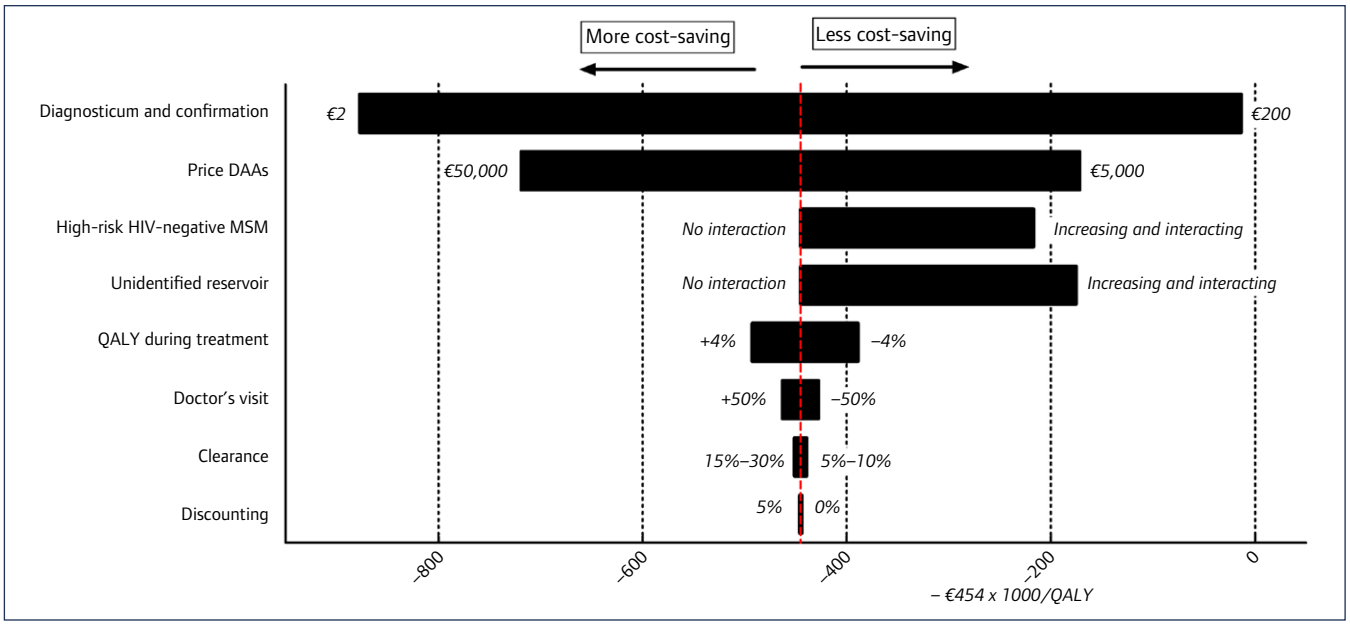

Figure 2. One-way sensitivity analysis of the incremental cost-effectiveness ratio (ICERs) (€/QALY). We compared the current situation with monitoring the high-risk group with an HCV-cAg test at 6-monthly time intervals and varied different key parameters. The bars show the range in ICER if these key variables are varied. All ICERs are stated in euros. DAA: direct-acting antivirals; EACS: European AIDS Clinical Society; HCV-cAg: HCV-core antigen; ICER: incremental cost-effectiveness ratio; MSM men who have sex with men; QALY: quality-adjusted life year

feeling of stigmatisation and criminalisation [63,64]. Yet previously infected patients have a higher risk of re-infection [17]. 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-positive 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 help to avoid losing patients out of the HCV care cascade [65]. This is less likely for HIV-infected MSM, who are integrated in HIV care, but more essential to other risk groups as HIV-uninfected MSM or PWIDs. In addition, a more sensitive monitoring approach is more feasible compared with intensified monitoring since the latter requires additionally hospital appointments.

The results of this study are of importance since the WHO recommends using cost-effectiveness analysis to determine the best value for money. In addition, there is a lack of financial resources towards testing and treatment of HCV [5,66]. In the past years most focus has been on the cost of DAAs and the cost-effectiveness of DAAs while little focus has been placed 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 [3,66]. 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 living with HCV by 2030, a target of the WHO, it important to assess the price of the diagnostic test [5]. Currently, the HCV-PCR is more costly (€105–€225) compared with the HCV-cAg test (€32), but both tests have a similar performance [38,39]. Therefore, the HCV-cAg test can play a significant role in HCV diagnosis 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 [8]. Nevertheless, the current overall price of HCV diagnosis 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 immediate DAA therapy [3,4]. 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 [21,67,68]. 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 upscaling of DAA therapy could result in micro-elimination [69]. 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 programmes 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 [4,15]. Therefore, our model is calibrated to complete and accurate data on the annual number of (newly) diagnosed HIV-positive MSM, which allows us to make accurate predictions on the epidemiological effect of alternative monitoring strategies and the possibility of achieving micro-elimination [3].

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-positive MSM, although HCV transmission is found less frequently among HIV-negative MSM [61,70,71]. HIV (PrEP usage could increase HCV incidence, as reported by some studies. This could result in HCV begin expanded among HIV uninfected MSM, with high-risk behaviour [61,72]. 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 MSM 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 who are not in care, for example PWIDs or "illegal" PrEP users, might result in new HCV infections among HIV-positive MSM [67,68]. 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 a cost increase but remained a cost-saving strategy.

Conclusion

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

Ethics approval

Not applicable.

Availability of data and material

The design of the model, the calibration and chosen parameters are documented in the supplement. Specific datasets generated and analysed during the study are available from the corresponding author on reasonable request.

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Conflicts of interest

SP: reports funding in the form of an unrestricted educational grant by Gilead Sciences [(NL-2018-000171) and grants from Gilead (215001269)], MSD (SDD 343462), ViiV Healthcare (14-0614-ViiV) and Janssen (771290). BEN, JJAvK and AV report no conflict of interests. CABB: reports grants from Gilead Sciences [(NL-2018-000171) and (215001269)], MSD (SDD 343462), ViiV Healthcare (14-0614-ViiV), Janssen (771290) and Boehringer (S14064/32844). DAMCvdV: reports grants from Gilead Sciences [(NL-2018-000171] and [215001269)], MSD (SDD 343462), ViivHealthcare (14-0614-ViiV) and Janssen (771290).

Authors' contributions

SP, CABB, BEN, DAMCvdV designed the model. SP, BEN, DAMCvdV programmed and analysed the model. SP, JVK, AV, CABB, BEN, DAMCvdV interpreted the results. SP wrote the first draft of the paper.

All authors critically revised and approved the final version of the manuscript.

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S1 Model description and calibration

The model is seeded in 2002 with 3800 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 and Table S2. All HCV transmission equations are described in Popping S *et al* [1]. Our model includes four activity groups [*i*] 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 who are infected but will clear HCV and five stages of increasing severity of fibrosis (METAVIR stages F0, F1, F2, F3 and F4). Stage F4 represents cirrhosis and is subdivided into compensated cirrhosis (F4C) and decompensated cirrhosis (F4D). Stage F0 makes a distinction between patients who are diagnosed in a timely manner and who initiated treatment, patients who 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 preformed with several tests, HCV antibodies, ALT, HCV-PCR and the HCV-core antigen depending on the scenario. In addition, monitoring intervals vary from every 6 months, every 3 months, and monthly. We targeted monitoring interventions to a high-risk group of patient 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 therapy is started.

Treatment was calibrated as follows: in the model until 2015, between 67% and 75% of patients with HIV who 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–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.

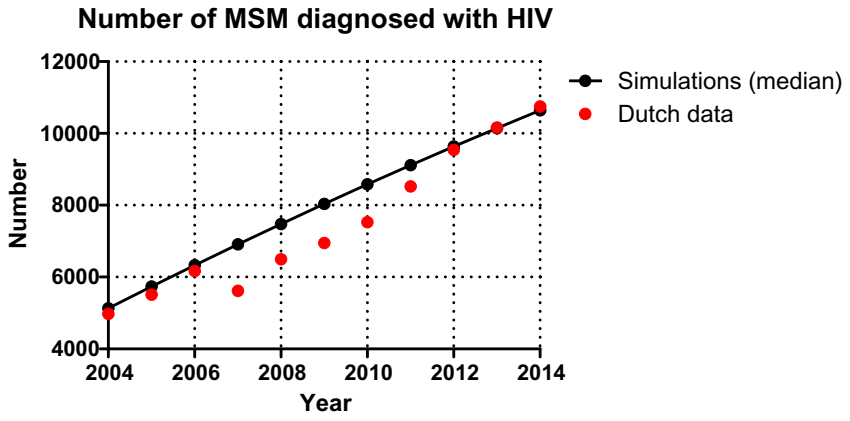
Parameters used for Monte Carlo filtering technique to calibrate our model

Table S1

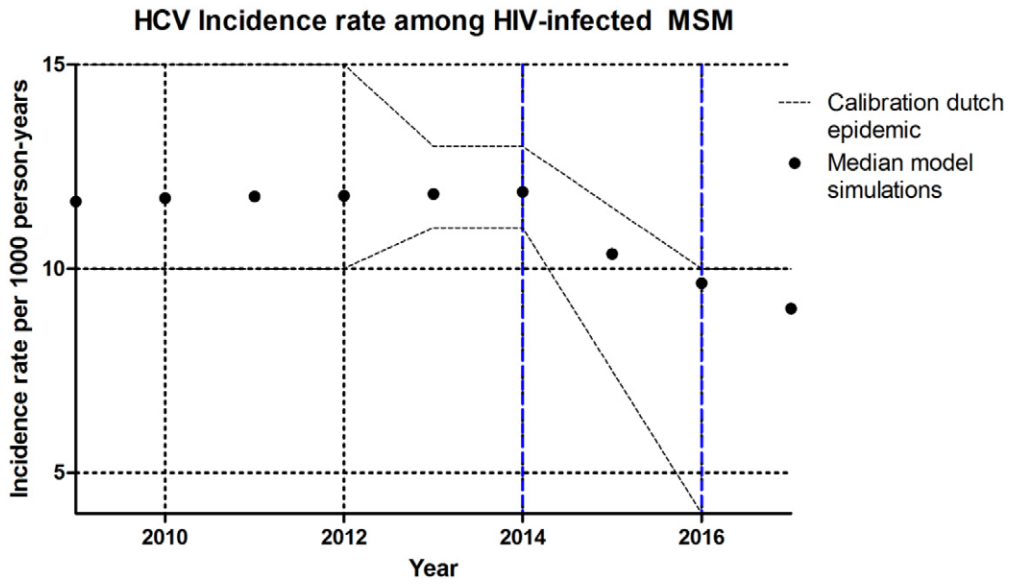
Parameter used to accept simulations	Values accepted	
Number of HIV-HCV co-infections in 2014 (*n*)	450–850	[2]
Annual number of new HIV-HCV co-infections (2014) (*n*)	100–150	[3]
Incidence rate in 2012–2014 (per 1000 person-years)	11–13 per	[4]
Incidence rate after DAA roll-out 2016 (per 1000 person-years)	4–10 per 1000	[5,6]
Re-infection rate in 2014 (% per year)	8–26.5	[7,8]

DAA: direct-acting antivirals; HCV: hepatitis C virus.

Variables used to calibrate and accept simulations



Comparison of the projected number of MSM who are diagnosed with HIV (black bullets and line) and the actual number of MSM diagnosed as reported by the Dutch HIV Monitoring Foundation.



Comparison of the incidence rate in 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, and in 2016 new incidence data were available [9].

S2 Model parameters used in hepatitis C transmission model

Table S2

Parameters of epidemic among HIV-positive MSM		Range
Annual new sexual partner per risk group [*i*] (*n*)	High	20–100§
	Medium	5–15
	Medium-low	1–4
	Low	0.1–0.9
Proportion per risk group	High	–0.14§
	Medium	–0.2
	Medium-low	0–0.3
	Low	0.4–0.9
Rate of assortative mixing		0–0.8§
Patients in stages F3, F4 in 2002 (%)		10%–30§

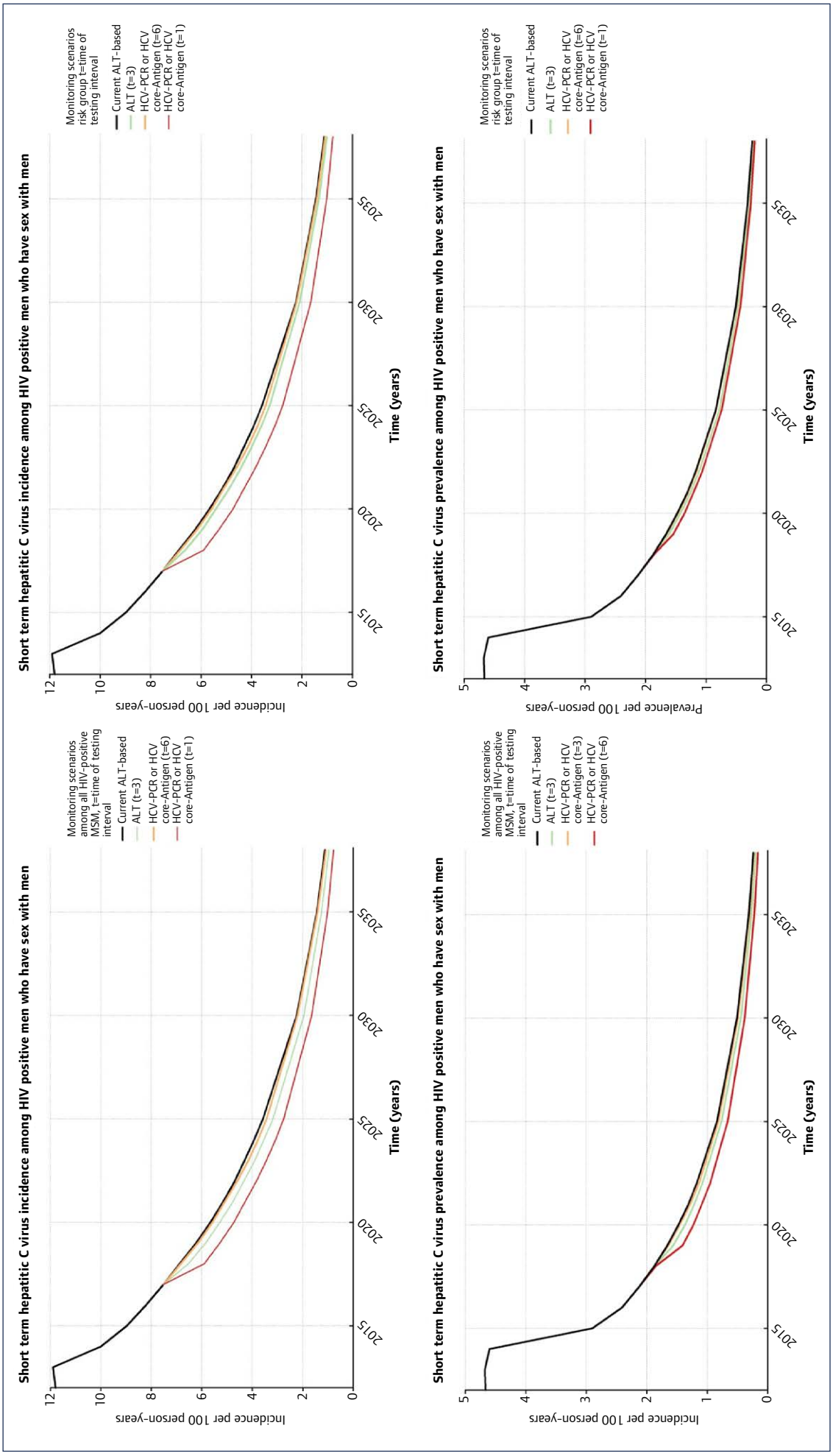
Life Expectancy and mortality	
Life expectancy HIV-infected men CD4 >350 (years)	80 [10]
Life expectancy HIV/HCV co- infected (F0–F3 stage) (years)	80
Life expectancy HIV/HCV co-infected compensated cirrhosis (per year)	0.024–0.055 [11]
Life expectancy HIV/HCV decompensated cirrhosis (per year)	0.019–0.35 [11]

Annual disease progression	
F0 to F1	0.098–0.122 [12]
F1 to F2	0.095–0.140 [12]
F2 to F3	0.097–0.159 [12]
F3 to compensated cirrhosis	0.098–0.135 [12]
Compensated to decompensated cirrhosis	0.029–0.063 [11]
Compensated to decompensated cirrhosis	0.029–0.063 [11]
Cirrhosis to hepatocellular carcinoma	0.01–0.03 [13]
Liver transplantations in HCV/HIV co-infected individuals	0

Cost	
Cost of hepatocellular carcinoma (including hospitalisation, treatment, surgery and care until death)	€67.591–€233.573 per patient [14,15]

HCV: hepatitis C virus; F0–F3 METAVIR score.
§ Calibrated.

S3 Short-term epidemiological impact of alternative monitoring strategies



In this figure the short-term epidemiological impact of the alternative monitoring strategies is projected. In the left panel the incidence and prevalence of HCV among HIV-infected MSM is projected when the alternative monitoring strategies apply to all HIV-infected MSM. Since this increases the cost of the total HCV epidemic, these strategies are not cost-effective. In the right panels the incidence and prevalence of HCV among HIV-infected MSM is projected when alternative monitoring strategies are targeted to a high-risk group of HIV-infected MSM who were previously HCV infected. This group has a high risk, with 20%–25% of becoming re-infected. Targeted testing with the HCV-core antigen costs less and has some impact on the incidence and prevalence. Therefore, this strategy is considered cost-saving.

S4 Outcome cost-effectiveness analysis

Table S4

Monitoring strategies	Lifetime costs per million (€)	Lifetime QALY×1000	ICER (*a*/*b*)×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	1689
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	9239
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)	2180 (2175–2186)	358	Dominated

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Supplementary references

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