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VIRAL HEPATITIS

Hepatitis C Virus Transmission Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: Modeling the Effect of Behavioral and Treatment Interventions

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The incidence of hepatitis C virus (HCV) infections among human immunodeficiency virus (HIV)-infected men who have sex with men has increased in recent years and is associated with high-risk sexual behavior. Behavioral interventions that target high-risk behavior associated with HCV transmission and treatment with direct-acting antivirals may prevent further HCV infections. We predicted the effect of behavioral and treatment interventions on HCV incidence and prevalence among HIV-infected men who have sex with men up to 2030 using a HCV transmission model parameterized with data from the Swiss HIV Cohort Study. We assessed behavioral interventions associated with further increase, stabilization, and decrease in the size of the population with high-risk behavior. Treatment interventions included increase in treatment uptake and use of direct-acting antivirals. If we assumed that without behavioral interventions high-risk behavior spread further according to the trends observed over the last decade and that the treatment practice did not change, HCV incidence converged to 10.7/100 person-years. All assessed behavioral interventions alone resulted in reduced HCV transmissions. Stabilization of high-risk behavior combined with increased treatment uptake and the use of direct-acting antivirals reduced incidence by 77% (from 2.2 in 2015 to 0.5/100 person-years) and prevalence by 81% (from 4.8% in 2015 to 0.9%) over the next 15 years. Increasing treatment uptake was more effective than increasing treatment efficacy to reduce HCV incidence and prevalence. A decrease in high-risk behavior led to a rapid decline in HCV incidence, independent of treatment interventions. *Conclusion:* Treatment interventions to curb the HCV epidemic among HIV-infected men who have sex with men are effective if high-risk behavior does not increase as it has during the last decade; reducing high-risk behavior associated with HCV transmission would be the most effective intervention for controlling the HCV epidemic, even if this was not accompanied by an increase in treatment uptake or efficacy. (HEPATOLOGY 2016;64:1856-1869).

SEE EDITORIAL ON PAGE 1834

The hepatitis C virus (HCV) epidemic in human immunodeficiency virus (HIV)-infected patients has evolved quickly over the past few years.[1-4] In Western countries, HCV is increasingly transmitted among HIV-infected men who have sex with men (MSM).[1,5-9] We observed, in the Swiss HIV Cohort Study (SHCS),[10] a steep rise in incidence of HCV infections among MSM without history of injection drug use. In contrast, HCV incidence stabilized among heterosexuals and decreased among people who inject drugs.[3]

An international network of HCV transmission among HIV-infected MSM was revealed by a phylogenetic study.[11] In this population, transmission is associated with high-risk behavior including condomless traumatic anal intercourse, fisting, use of recreational drugs, and group sex.[1,3,7,12,13] In the SHCS, the increase in HCV incidence coincided with reduced self-reported condom use among MSM on antiretroviral therapy (ART).[14]

Effective interventions to curb the HCV epidemic among HIV-infected MSM remain to be established. Behavioral interventions that target high-risk sexual practices associated with HCV transmission may prevent new HCV infections. Because recently introduced treatments for HCV with second-generation direct-acting antiviral agents (DAAs) rapidly reduce HCV viral load and achieve high cure rates, they offer an unprecedented opportunity to prevent transmissions.

In this study, we analyzed data from the SHCS to develop a mathematical model of HCV transmission among MSM who do not inject drugs. We used the model to replicate the HCV epidemic in Switzerland and to estimate the effect of behavioral and treatment interventions on HCV incidence and prevalence up to 2030.

Subjects and Methods

THE SWISS HIV COHORT STUDY

The SHCS is a nationwide, prospective cohort that enrolls HIV-infected patients, aged 16 or above, since 1988, drawing from Swiss university hospitals, cantonal reference hospitals, and private practices.[10,15] Written informed consent is mandatory for inclusion in the SHCS, and the study has been approved by all local ethics committees. The SHCS includes 73% of HIV-infected patients declared to the Swiss public health authorities.[16] Clinical, behavioral, and laboratory data are collected at enrollment and at follow-up visits every 6 months. The collected data include information on antiretroviral and HCV treatments, sexual preferences, condom use, and sex with stable and occasional partners.[15] HCV-seronegative patients were screened biannually for HCV infection between 1998 and 2006 and yearly thereafter. Immunoblotting confirmed positive results by third-generation enzyme-linked immunosorbent assay. We included all HCV-seronegative MSM who had at least one follow-up HCV antibody measurement after January 2000. Patients with a positive HCV serology at entry, those who seroconverted before 2000, and those who reported injecting drug use during the follow-up period were excluded from the incidence analysis. For the estimation of the incidence that we used to fit the model, the follow-up period ended at the first positive HCV serology or the last negative serology as described previously.[3] For the analyses on sexual behavior, the follow-up period ended at dropout or death.

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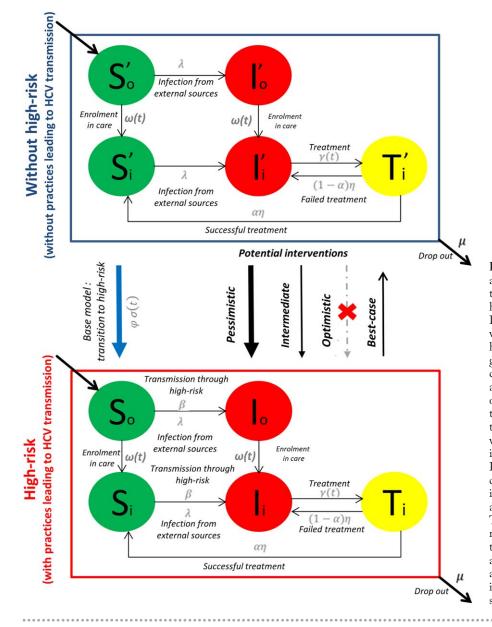Tel: +41-31-631-35-15

FIG. 1. Model structure. Individuals are distributed in groups according to their risk behavior (without and with high-risk) and enrollment in HIV care. Individuals switch from the group without high-risk to the group with high-risk at rate $\phi\sigma(t)$ and from the group out of care to the group in HIV care at rate $\omega(t)$. Susceptible individuals may be infected by an external force of infection (λ) that accounts for infections not acquired by contacts within the modeled population. Individuals within the high-risk group may also infect each other at an infection rate β. Individuals with spontaneous HCV clearance remain susceptible. Infected individuals without spontaneous clearance start HCV treatment at rate $\gamma(t)$. Treatment lasts on average $1/\eta$ and results in HCV clearance for a proportion α of all treated patients. Individuals exit the system at rate μ from all compartments. Abbreviations: I, infected; i, in care; o, out of care; S, susceptible; T, on treatment.

HCV TRANSMISSION MODEL

We adopted a system of ordinary differential equations to model HCV transmission among HIV-infected MSM (Supporting Information). We set out to reproduce HCV incidence among HIV-infected MSM in Switzerland between 2000 and 2013 by classifying the population into compartments distributed by stage of infection, risk groups and enrollment in care. Risk groups included (1) individuals who do not engage in sexual practices associated with HCV transmission

(group without high-risk behavior) and (2) individuals who do engage in sexual practices associated with HCV transmission (group with high-risk behavior). Each risk group includes five compartments: (1) two HCV-uninfected (susceptible) "in" and "out" of HIV care (referred to as "in care" and "out of care" from now on); (2) two HCV-infected in and out of care; and (3) one on treatment for HCV only accessible for individuals in care. The model structure is summarized in Fig. 1. Out of care individuals can enter the in care category at a rate $\omega(t)$. Newly HIV-infected MSM enter the out of care

susceptible category at a rate that varies over time $\rho(t)$. A fraction $\phi\psi(t)$ of these individuals enter the susceptible compartment in the high-risk group, where $\psi(t)$ is the proportion of newly HIV-infected MSM who have unprotected sex with occasional partners, which we term unsafe sex; and ϕ is the proportion of these individuals who also engage in high-risk behavior and therefore are at risk of HCV transmission. High-risk behavior comprises condomless traumatic anal intercourse, fisting, use of recreational drugs, and group sex. ϕ is referred to as the *high-risk/unsafe sex ratio*. The remaining newly HIV-infected MSM enter the susceptible compartment in the group without high-risk. Individuals switch from the group without high-risk to the high-risk group at a rate $\phi\sigma(t)$, where $\sigma(t)$ is the rate at which individuals start to have unsafe sex. We refer to $\psi(t)$ and $\sigma(t)$ as *high-risk recruitment parameters*. All susceptible individuals may be infected by an external force of infection λ that accounts for infections unrelated to high-risk contacts within the modeled population. Because λ affects all individuals, incidence is always $\geq\lambda$ irrespective of interventions. Individuals within the high-risk group infect each other at an infection rate β. This rate is associated with the probability of establishing an infection given an infectious contact. Infected individuals in both risk groups start treatment at a rate $\gamma(t)$. The mean duration of treatment is $1/\eta$ and results in HCV clearance for a fraction α of treated individuals. Individuals who clear the infection are again susceptible. Individuals exit the system at a rate μ from all compartments, which indicates the end of their sexual activity in Switzerland. We accounted for reinfections and naive infections by splitting this model. The resulting model ("reinfection model") is equivalent to the main one, and its structure is displayed in Supporting Fig. S1.

MODEL PARAMETERIZATION

Most parameters were measured from SHCS data. The *high-risk/unsafe sex ratio* (ϕ), the proportion of individuals out of care, and the change in diagnosis rate over calendar year were estimated from published data; the infection rate β and the assortativity coefficient were fitted to the incidence data by maximum likelihood (Supporting Information).

We obtained the numbers of newly susceptible individuals $\rho(t)$ from the SHCS database and the proportion of HIV-infected MSM out of the SHCS. These numbers were based on new registrations into the cohort. We used Bayesian Poisson regression models[17,18] to estimate entrance rates from these numbers.

HCV treatment rates were determined separately for the periods 2000-2005 and 2006-2013 because treatment uptake substantially increased between those periods in the SHCS.[19] We modeled this transition as a logistic function (Supporting Information). Initial conditions were also approximated from data, namely, the numbers of patients susceptible, infected, and on treatment for HCV at the beginning of 2000. We used SHCS information on self-reported unprotected sex with occasional partners to estimate two time-dependent *high-risk recruitment parameters*: (1) the proportion of patients who reported unsafe sex $\psi(t)$ during their second follow-up visit, which we consider to reflect their sexual behavior following HIV diagnosis, and (2) the rate $\sigma(t)$ at which patients without unsafe sex at the beginning of the follow-up started to engage in this practice.

We estimated the fraction of patients out of care by combining data from the European Men-Who-Have-Sex-With-Men Internet survey[20] and a modeling study on HIV transmission among MSM in Switzerland.[21] We found transition rates from HIV infection to enrollment in care that led the model to reproduce this fraction by assuming that the rates reflected the increase estimated by van Sighem et al.[21]

Uncertainty analyses were based on Latin hypercube sampling. We sampled the infection rate β, the exit rate μ, and the external force of infection λ to produce combinations of parameters using this technique. We then obtained model solutions for each combination to determine 95% confidence intervals (CIs) (Supporting Information).

INTERVENTIONS TO REDUCE HIGH-RISK BEHAVIOR AND TREATMENT SCENARIOS

We projected future HCV incidence based on hypothetical interventions that reduce high-risk behavior and increase treatment uptake and/or efficacy. Projections of the *high-risk recruitment parameters* were based on observed trends. Behavioral interventions included three scenarios. (1) *Pessimistic scenario*: no intervention, in which the size of the high-risk group grows further according to the trend observed in the SHCS over the last decade. In this scenario an increasing number of patients enter the high-risk group, until high-risk recruitment parameters duplicate the last observation; thereafter, they saturate. (2) *Intermediate scenario*: health promotion or autonomous saturation leading to a stable size of the high-risk group. (3) *Optimistic scenario*:

health promotion or autonomous saturation leading to a decreasing size of the high-risk group. In this scenario, no more patients enter the high-risk category. Treatment interventions included use of DAAs and increased treatment uptake. We considered two scenarios for treatment uptake, according to treatment rate: (1) remained constant at the observed average between 2006 and 2013 (22% per year) and (2) increased to 100% per year; i.e., the average time from infection to treatment was reduced to 1 year. Our model also compared the impact of DAAs[22,23] with interferon-based treatments.[24] The average duration of interferon-based treatment was assumed to be 9 months and to result in 53% sustained virologic response, as observed in the SHCS.[19] Treatment with DAAs was assumed to last 3 months on average and to result in 90% sustained virologic response, independent of HCV genotype.[22,23] We reported predicted incidence and prevalence curves by combining these scenarios.

In a further analysis, we assessed a best-case scenario of risk behavior. In this analysis we accelerated the decrease in the size of the high-risk group associated with the optimistic scenario. We assumed that individuals in the high-risk group transit to the group without high-risk at a rate that equals the last observed rate of transition from the group without to the group with high-risk behavior. This approximation aims to reflect the speed of behavioral change observed in the population.

SENSITIVITY ANALYSIS I: DIFFERENT HIGH-RISK/UNSAFE SEX RATIOS

The approximated value for the *high–risk/unsafe sex ratio* that we used in the main analyses (0.25 as observed in Schmidt et al.[13]) may not accurately reflect the reality as it does not include all sexual practices leading to HCV transmission. We therefore performed model fits and projections for all scenarios, where this ratio increased in steps of 0.05 from 0.2 to 0.4.

SENSITIVITY ANALYSIS II: IMPORTED INFECTIONS

In this analysis we assumed that an increasing percentage of incident HCV infections observed in the high-risk group were not acquired by contact with other HIV-infected MSM in Switzerland (imported infections). We performed model fits and projections for all scenarios, where the percentage of imported infections increased from 3% to 27%. These values

TABLE 1. Characteristics of All MSM Registered in the SHCS Who Were Included in the Parameterization of the Model

Total number of patients	5,052
Age at registration (median [IQR])	37 (31-44)
Follow up time (years, median [IQR])	7.8 (3.6-14.9)
ART	
Yes	4,619 (91.4%)
No	433 (8.6%)
CD4 cell count at ART start (cells/μL, median [IQR])	268 (156-389)
Viral load at ART start (log$_{10}$ copies/mL, median [IQR])	4.8 (4.2-5.3)
Intravenous drug use*	127 (2.5%)
Information on sexual partners	
Sex with stable partners (n [%])	
Yes	3,655 (72.3%)
No	1,257 (24.9%)
Refuse to answer	91 (1.80%)
Missing	49 (0.97%)
Condom use with stable partner (n [%])	
Inconsistent or never†	2,080 (56.9%)
Refuse to answer	29 (0.8%)
Missing	1 (0%)
Sex with occasional partners (n [%])	
Yes	3,860 (76.4%)
No	975 (19.3%)
Refuse to answer	168 (3.3%)
Missing	49 (1.0%)
Condom use with occasional partner (n [%])	
Inconsistent or never†	1,860 (48.1%)
Refuse to answer	40 (1.0%)
Missing	2 (0.0%)

*Out of all MSM. These patients were excluded from the analyses.
†Ever reported.
Only patients with available questionnaires on sexual partners who were followed beyond 2000 were included.

were achieved by assuming increasing external forces of infections λ in the high-risk group.

SENSITIVITY ANALYSIS III: PROTECTIVE EFFECT OF PREVIOUSLY CLEARED HCV INFECTION

Some studies suggest that the risk of reinfection after clearance may be lower than the risk of infection in naive individuals.[25] We assessed the effect of this potential protective effect by assuming that the probability of HCV transmission given an infectious contact is lower in individuals who have cleared HCV than in naive individuals. We performed model fits and projections for all scenarios, where the probability of reinfection was reduced by 13%, 25% (as in Martin et al.[26]), and 50%.

All procedures, including calibration, fitting algorithms, and uncertainty analyses, were implemented in R.[27] Differential equations were solved with the R package deSolve.[28,29]

TABLE 2. Model Parameters Used to Reproduce the Incidence Observed Between 2000 and 2013

Parameter	Definition	Value	Functional form	Source
$\omega(t)$	Rate of enrollment in care (from HIV infection, per year)	0.45 before 2005 0.58 after 2005		Estimation using data from van Sighem et al.[21]
$\rho(t)$	New HCV-uninfected MSM rate[*,†] (individuals per year/0.8)	(135-257)	Splines smoothing of a seriesof yearly rates	SHCS
$\psi(t)$	Proportion of individuals with unsafe sex at entry[‡]		3.2×10^{-2} if $t \leq 3.8$ $6.1 \times 10^{-2} - 1.6 \times 10^{-2}\, t + 2.5 \times 10^{-3}\, t^2 - 7.2 \times 10^{-5}\, t^3$ if $3.8 < t < 13.5$	SHCS
ϕ	High-risk/unsafe sex ratio[§]	0.25		[13]
$\sigma(t)$	Rate at which individuals start to have unsafe sex (per year)[‡]		$4.1 \times 10^{-2} + 2 \times 10^{-3}(t + 1.5) - 1.4 \times 10^{-3} (t + 1.5)^2 + 1.2 \times 10^{-4}(t + 1.5)^3$	SHCS
β	Infection rate (95% CI, per year)	5.1 (4.3-5.7)		Fit
α	Proportion of patients who clear infection after treatment[‖]	0.53		SHCS [19]
η	1/average treatment duration (per year)	4/3		SHCS
λ	External force of infection $\times 10^{-3}$ (per year)[¶]	2.3		SHCS
μ	Exit rate (95% CI)	0.049 (0.045-0.053)		SHCS
$\gamma(t)$, $\gamma'(t)$	Rate of treatment for each risk group (per year)	(0.02-0.22)	$0.2/(1 + e^{-t+2006}) + 0.02$	SHCS
$S_{2000} + S'_{2000}$	Initial number uninfected patients[†,#]	1,552		SHCS
I_{2000}	Initial number of infected patients[†,#]	8		SHCS
T_{2000}	Initial number of patients on treatment[†,#]	0		SHCS

*Rates were obtained applying Bayesian Poisson regression models with nonparametric smoothing priors using the R package INLA.[17]

†Scaled to the HIV-infected MSM population in Switzerland assuming that 80% of all individuals in this population enroll in the SHCS.

‡The origin is 2000.

§Ratio between the number of patients who reported frequent bondage, dominance/submission, sadism/masochism, or fisting and those who reported unprotected anal intercourse with nonsteady partners. The approximated ratio between patients who reported skin damage with bleeding and those who reported unprotected anal intercourse with nonsteady partners is 0.23.

‖Weighted average according to time from diagnosis to treatment initiation.

¶1999-2000 average incidence rate.

#Initial value in year 2000.

Abbreviations: I, infected; S, susceptible; T, on treatment.

Results

STUDY POPULATION

A total of 5,052 MSM were included in the analyses (Table 1). Median age at registration in the SHCS was 37 years (interquartile range [IQR] 31-44). Ninety-one percent of all patients started ART during the follow-up time. Sex with occasional partners was reported by 3,860 (76%) MSM, of whom 1,860 (48%) also reported inconsistent condom use.

MODEL PARAMETER ESTIMATES

Model parameters used to reproduce observed HCV incidence in the SHCS are shown in Table 2.

An average of 190 HCV-negative MSM newly diagnosed with HIV and without history of intravenous drug use were enrolled into the cohort per year (Supporting Fig. S2A). The proportion of patients who reported unsafe sex during their second follow-up visit was 5% in 2000 and increased continuously to reach 13% in 2013 (Fig. 2A). The transition rate to unsafe sex rose from 0.04 per year in 2000 to 0.13 per year in 2012 (Fig. 2B). We assumed that a fraction (0.25) of patients who engage in unsafe sex also engage in high-risk behavior. This approximation reflects the ratio between the number of patients who reported frequent bondage, dominance/submission, sadism/masochism, or fisting and those who reported unprotected anal intercourse with nonsteady partners in Schmidt et al.[13] The percentage of patients treated for HCV was 11% before 2006 and rose to 42%
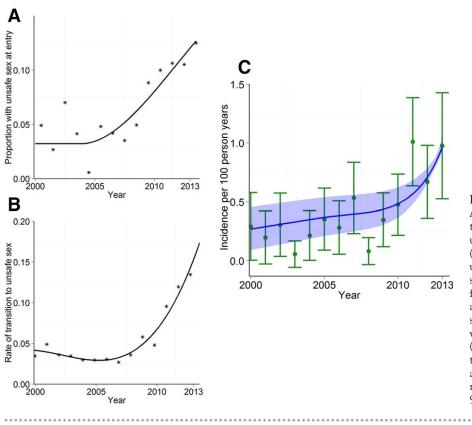
FIG. 2. *High-risk recruitment parameters* and HCV incidence. (A) Proportion of new individuals who have unprotected sex with occasional partners (unsafe sex). (B) Rate at which individuals start to have unsafe sex. (black stars, observed; continuous black line, functional fit). The model assumed that a fraction of the patients with unsafe sex also engage in high-risk behavior, which can result in HCV transmission. (C) HCV incidence rates observed in the SHCS (green dots and error bars) and obtained with the transmission model (continuous blue line; shaded, 95% CIs).

between 2006 and 2013. Consistently, when we compared the periods 2000-2005 and 2006-2013, the average treatment rate increased by a factor of 10: 2% per year in the earlier period versus 22% per year in the later period (Table 2). The exit rate estimated from patients who died or left Switzerland, as specified in the cohort, was 0.049 (95% CI 0.045-0.053), which implies an average time of over 20 years of sexual activity. We estimated that on average 84% of HIV-infected MSM were in care between 2000 and 2010. Associated rates of enrollment in care were found to be 0.45/year and 0.58/year before and after 2005 respectively. These rates imply times from HIV infection to enrollment in care of 2.2 and 1.73 years, respectively. Supporting Fig. S3 shows the likelihood curve for the estimated rate of infection.

OBSERVED AND MODELED HCV INCIDENCE, 2000-2013

Modeled HCV incidence accurately reproduces observed HCV incidence (Fig. 2C). It increased from

0.2/100 person-years (py) in 2000 to 1.0/100 py in 2013.

IMPACT OF INTERVENTIONS TO REDUCE HIGH-RISK SEXUAL BEHAVIOR AND TREATMENT SCENARIOS, 2015-2030

Pessimistic Scenario: Growing Size of the High-Risk Group

If the spread of high-risk practices associated with HCV transmission was unchecked, the model predicted a steep increase in HCV incidence and prevalence. Incidence converged to 10.7/100 py if treatment practice remained unchanged (upper panel, Fig. 3A). If treatment uptake increased considerably, incidence continued to rise at a lower rate than with the current treatment practice, to reach 10.4/100 py and 8.5/100 py in 2030 with and without DAAs, respectively (upper panel, Fig. 3A). Interestingly, the highest predicted incidence was observed in the
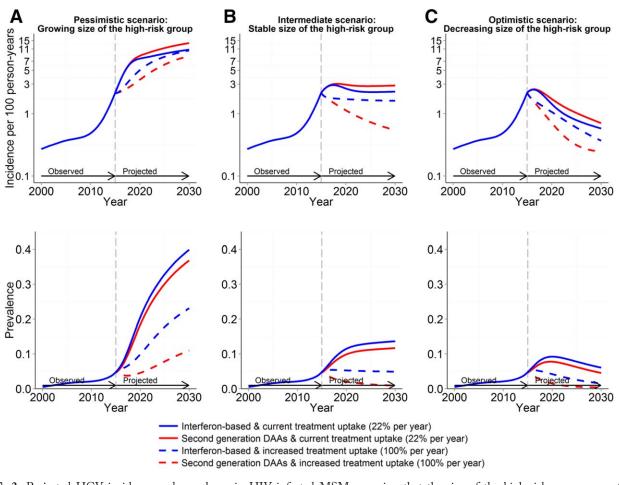
FIG. 3. Projected HCV incidence and prevalence in HIV-infected MSM assuming that the size of the high-risk group grows (A), and health promotion or autonomous saturation leading to (1) stable size of the high-risk group (B) and (2) decreasing size of the high-risk group (C). Two scenarios of future treatment uptake were included: (1) treatment rate constant at the average between 2006 and 2013 (22% per year, continuous lines) and (2) increased treatment rate (100% per year, dashed lines). Two treatment alternatives are displayed: second-generation DAA regimens (red) and interferon-based regimens (blue). Dashed, gray, vertical lines indicate the beginning of the projection period.

scenario with current treatment uptake and DAAs. A combination of two factors explains this behavior: firstly, short-duration effective treatments led to rapidly cured infections, which in turn resulted in an enlarged size of the susceptible group; and secondly, the treatment rate was not large enough to contain transmission. This outcome was observed in all scenarios.

Prevalence also increased rapidly in this scenario. Without change in treatment uptake, it was above 36% in 2030 irrespective of the type of treatment. But if treatment uptake increased considerably, prevalence in 2030 was 23.1% and 11% without and with DAAs, respectively (lower panel, Fig. 3A). The model also predicted that in 2030 reinfection will account for at

least 44% of all incident infections (versus 3.6% in 2015; Supporting Table S1)

Intermediate Scenario: Stable Size of the High-Risk Group

Stabilization of high-risk behavior without change in treatment uptake led to a rapidly saturated incidence at around 2.6/100 py if treatment uptake did not change. If treatment uptake increased considerably, DAAs led to a continuous decline in incidence, reaching 0.5/100 py in 2030 (upper panel, Fig. 3B). The benefit of DAAs compared to interferon-based therapy was largest in this case. Prevalence displayed a similar pattern. It stabilized at around 12.7% if treatment
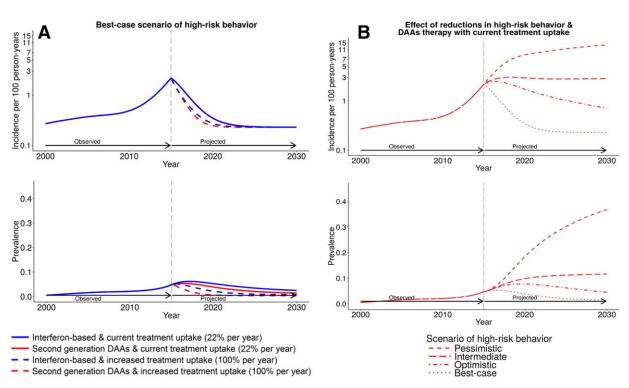
FIG. 4. (A) Projected HCV incidence (upper panel) and prevalence (lower panel) in HIV-infected MSM assuming that no additional individuals enter the high-risk group and that individuals in the high-risk group transit to the group without high-risk at a rate that equals the last observed rate of transition from the group without high-risk behavior to the group with high-risk behavior. Two scenarios of future treatment uptake were included: (1) treatment rate constant at the average between 2006 and 2013 (22% per year, continuous lines) and (2) increased treatment rate (100% per year, dashed lines). Two treatment alternatives are displayed: second-generation DAA regimens (red) and interferon-based regimens (blue). Dashed, gray, vertical lines indicate the beginning of the projection period. (B) Effect of reductions in high-risk behavior when assuming treatment with DAAs and current treatment rate.

uptake did not change and decreased considerably to reach 0.9% at the highest treatment uptake with DAAs (lower panel, Fig. 3B). The model also predicted that in 2030 reinfection will account for at least 23% of all incident infections (Supporting Table S1).

Optimistic Scenario: Decreasing Size of the High-Risk Group

A reduction in the frequency of high-risk practices associated with HCV transmission led to an immediate decrease in incidence, regardless of treatment uptake and type of treatment (upper panel, Fig. 3C). In this scenario, introducing DAAs had only a modest influence on incidence and prevalence. As expected, the minimal incidence and prevalence predicted in this study were achieved in this scenario when DAAs were introduced at the highest treatment uptake (incidence 0.2/100 py, prevalence 0.4% in 2030; lower panel, Fig. 3C). The model predicted that in 2030 reinfection

will account for at least 7.6% of all incident infections (Supporting Table S1).

Best-Case Scenario: Rapidly Decreasing Size of the High-Risk Group

In this scenario, the model predicted an immediate steep decline in HCV incidence (upper panel, Fig. 4A). In 2025 incidence saturated at 0.2/100 py irrespective of treatment interventions. Prevalence also declined considerably in this scenario. It ranged between 2.5% and 0.4% in 2030 (lower panel, Fig. 4A).

Figure 4B shows HCV incidence and prevalence associated with different scenarios of high-risk behavior when assuming treatment with DAAs and current treatment rate.

In all scenarios, incidence was more sensitive to the considered changes in treatment uptake than to changes in treatment efficacy (Fig. 3). Trends for high-risk recruitment parameters in the first

two behavioral scenarios are displayed in Supporting Fig. S4. Supporting Table S2 shows changes in high-risk behavior associated with each scenario.

SENSITIVITY ANALYSIS I: DIFFERENT HIGH-RISK/UNSAFE SEX RATIOS

Projected HCV incidence with all interventions assuming increasing *high-risk/unsafe sex ratios* (i.e., increasing the proportion of patients with unsafe sex who also engage in high-risk behavior) are shown in Supporting Fig. S5. In the pessimistic case scenario of risk behavior, the model predicted higher incidence and prevalence with increasing *high-risk/unsafe sex ratios*. Incidence in 2030 ranged from 8.2/100 py to 20.5/100 py and prevalence from 10.6% to 51.2%, with ratios of 0.2 and 0.4, respectively (left panels, Supporting Fig. S5). Consistently, in the intermediate and optimistic scenarios of risk behavior, predicted incidence stabilized at higher values as *high-risk/unsafe sex ratios* increased (center and right panels, Supporting Fig. S5). Despite these differences, the effects of all interventions were equivalent to those described in the main analysis.

SENSITIVITY ANALYSIS II: IMPORTED INFECTIONS

Behavioral and treatment interventions were also effective at decreasing HCV incidence and prevalence when the proportion of infections assumed to be imported increased. When this proportion was set to be maximal (27%) in the intermediate scenario of risk behavior, increased treatment uptake and efficacy led to incidence and prevalence reaching 0.7/100 py and 1.1% in 2030, respectively (Supporting Table S3). The goodness of the fit decreased as more infections observed in the high-risk group were assumed to be imported, suggesting a predominant role of domestic transmission. Worsening fits may lead to unrealistic projections, especially in the pessimistic scenario because the model becomes less capable of reproducing the observed increase in incidence.

SENSITIVITY ANALYSIS III: PROTECTIVE EFFECT OF PREVIOUSLY CLEARED HCV INFECTION

Predicted HCV incidence and prevalence decreased as the reduction in reinfection probability increased (Supporting Table S4). Incidence and prevalence displayed the same pattern observed in the main analysis (Supporting Fig. S6). In the pessimistic scenario, with a 25% reduction in reinfection probability, treatment with DAAs at the highest treatment uptake led to 5.5/100 py incidence (versus 8.5/100 py in the main analysis) and 7.6% prevalence (versus 11.0% in the main analysis). Despite these variations, the effect of all interventions was equivalent to that described in the main analysis, even when the protective effect was strong.

Discussion

We reconstructed the HCV epidemic among HIV-infected MSM in Switzerland between 2000 and 2013 using a mathematical transmission model based on two risk groups. We used this model to predict the future course of HCV incidence and prevalence in HIV-infected MSM. Different modeled scenarios based on hypothetical behavioral and treatment interventions showed that prevention of high-risk behavior alone could result in considerably reduced HCV transmission.

The model showed that substantially increasing only treatment uptake would more effectively reduce HCV incidence and prevalence than substantially increasing only treatment efficacy. There are fewer contraindications to DAAs-based treatments than to interferon-based treatments, so DAAs-based treatments may improve uptake. The model predicts that if high-risk behavior continues to increase according to the trends observed during the last decade, HCV incidence will continue to rise, despite increasing treatment uptake and efficacy. However, stabilization of high-risk behavior combined with a considerable increase in treatment uptake and efficacy could effectively reduce HCV incidence and prevalence. Moreover, the benefit of DAAs over interferon-based therapy was highest in this stable scenario when assuming high treatment uptake. Reduction in high-risk behavior could lead to a rapid decline in incidence within the next few years, independently of improved treatment uptake or efficacy. The model predicted that reinfections will account for an increasing proportion of all incident infections in the future. This is in line with recent studies that have reported high rates of reinfection.[30,31]

STRENGTHS AND LIMITATIONS

A major strength of our analysis is that we estimated most model parameters directly by using patient-level data from the SHCS.[10,15] Most parameters corresponded to a single population, so they were internally consistent. The inclusion of data on the evolution of sexual behavior among HIV-infected MSM over the last decade was an additional strength of our model. These data reveal heterogeneity,[32] which we captured by splitting the population into two risk behavior groups.

Due to the lack of data on specific high-risk practices, we had to assume that the proportion of people with high-risk behavior was a constant fraction of the population that engages in unsafe sex. We believe this is a reasonable approximation to reality which allowed us to take advantage of the available data on sexual behavior. This quantity was based on published observations,[13] which may have led to an underestimation of this fraction as it does not include all practices that are believed to result in HCV transmission. However, a sensitivity analysis which considered several values of this parameter resulted in concordant predictions. Another limitation was that we did not explicitly model the link between sexual behavior and recreational intravenous drug use, which is increasingly recognized as a risk factor for HCV transmission among MSM[12,33] and may contribute to the HCV epidemic. We did not include HIV-uninfected MSM in the modeled population, but we think this was reasonable: a recent Swiss survey showed that the prevalence of HCV in HIV-uninfected MSM was only 0.4%, thus not higher than that in the general population.[34] Our approximation was based on the fact that there is no evidence of boosted HCV transmission among HIV-negative MSM. The reason HCV transmission seems to be confined to HIV-infected MSM is unknown. Serosorting (the practice of using HIV status as a decision-making point in choosing sexual partners) is common but not generalized,[35] and its role in the spread of HCV among HIV-infected MSM remains uncertain. Further factors, including HIV-mediated impairment of mucosal immunity, which is often not completely restored during ART, may also play a role. Importantly, the scale-up of HIV preexposure prophylaxis may reduce serosorting, which in turn could result in an HCV transmission bridge from HIV-positive to HIV-negative MSM.

Little is known about risk behavior patterns and demographics of people with undiagnosed HIV infections. However, 80% of HIV-infected MSM living in Switzerland are estimated to be enrolled in the SHCS.[16] Therefore, the data we used to parameterize this model are likely to be representative of this population.

The main model assumed a constant external force of infection. Although the frequency of drug injection among MSM in the SHCS was low (only 2.5% ever reported) and stable over the study period (results not shown), which supports our assumption, we undertook a sensitivity analysis to evaluate the impact of increasing the external force of infection in the high-risk group. These increases are equivalent to more infections acquired by high-risk contacts outside the modeled population (imported infections). The model predictions suggested that behavioral and treatment interventions can effectively reduce incidence and prevalence even when the number of imported infections is large. Our conclusions also remained unchanged when assuming that HCV clearance reduces the risk of subsequent infections (protective effect). In this study, we did not explore alternative explanations for increased HCV transmissions over time, such as the emergence of more transmissible HCV strains. However, previous phylogenetic analyses revealed that many different HCV strains were involved in its spread among HIV-infected MSM,[11,36] so the emergence of a particularly transmissible HCV strain is unlikely to be the main driver of the epidemic. Finally, assuming that risk behavior will continue to increase at the speed it has over the last years (as we did in the pessimistic scenario) may have led to unrealistically large sizes of the population with high-risk behavior and resulted in a very high prevalence for the pessimistic scenario. This and the best-case scenario are extreme cases that bound the possible future outcomes of the HCV epidemic. Our results may not apply to populations of HIV-infected MSM where HCV incidence has not increased because these populations may not have the same demographic, clinical, and behavioral characteristics[37] as the population we studied. But HCV incidence has recently increased among HIV-infected MSM in many settings, as synthesized in a meta-analysis.[9]

In this study, we did not use viral sequence data to trace HCV transmissions. A recently published phylogenetic analysis in the SHCS[38] revealed that people with closely related HIV viruses were more likely to acquire HCV infection if their phylogenetic neighbors were HCV-infected. These HIV and HCV transmission networks within the SHCS underscore the role of

domestic HCV transmission linked to sexual risk behavior. Therefore, public health interventions might reduce HCV transmission even if these are only implemented locally.

COMPARISON WITH OTHER STUDIES

We believe ours is the first published modeling study to (1) use data on changes in high-risk behavior to account for changes in HCV incidence among HIV-infected MSM; (2) evaluate the effects of trends in high-risk behavior on the course of the HCV epidemic, independently of treatment intensification; and (3) incorporate longitudinal data on sexual behavior and routine HCV screening together with HCV treatment uptake and outcomes. Martin et al.[39] recently modeled the HCV epidemic among HIV-diagnosed MSM in the United Kingdom and found that scaling up DAAs in this setting could substantially reduce HCV prevalence without behavioral interventions, but they studied a population with stable primary HCV incidence, while primary HCV incidence has increased in the SHCS and in other settings over the last decade.[3,9] Martin et al. did not include data on the evolution of high-risk behavior or assess the role of changing high-risk behavior, independently of treatment intensification. Because changes in high-risk behavior drive the surging HCV epidemic and are a key target for interventions, we based our predictions on potential scenarios of high-risk behavior. In contrast with the study by Martin et al., our results suggest that in settings where HCV incidence is rising, scaling up treatment cannot revert the HCV epidemic if high-risk behavior continues to spread as it has over the last decade.

IMPLICATIONS OF FINDINGS

Our model suggests that the most effective strategy for controlling the HCV epidemic among HIV-infected MSM is to adopt health promotion interventions that limit high-risk behavior. Targeted interventions to curb the HCV epidemic, such as increasing access to treatment, are effective if accompanied by interventions or autonomous saturation that slow the spread of high-risk behavior. Of note, self-reported unsafe sex does not reflect all high-risk sexual practices associated with HCV transmission that are not recorded in the SHCS. Self-reported unsafe sex rather served as a proxy for high-risk behavior. The good fit of the model predictions to the incidence data suggests that self-reported unsafe sex is associated with other high-risk sexual practices. Trends in self-reported unsafe sex might therefore predict the future course of HCV infections and guide interventions to reduce HCV incidence. The results of this study could be used to inform public health policy intended to prevent HCV transmission among HIV-infected MSM.

The validity and scope of our findings must be determined in clinical trials or observational studies. These model projections are based on hypothetical representative outcomes of interventions to reduce high-risk behavior (pessimistic, intermediate, optimistic, and best), but real-world interventions are likely to cluster around the intermediate scenario. Cost-effectiveness analyses that consider realistic outcomes of behavioral interventions are also required to guide implementation of public health interventions intended to reduce transmission of HCV among HIV-infected MSM.

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