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MAJOR ARTICLE

High Number of Potential Transmitters Revealed in a Population-based Systematic Hepatitis C Virus RNA Screening Among Human Immunodeficiency Virus-infected Men Who Have Sex With Men

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Background. The proportion of undiagnosed hepatitis C virus (HCV) infections in high-risk populations, such as human immunodeficiency virus (HIV)–infected men who have sex with men (MSM) is unclear. Identification of potential HCV transmitters is important to reach World Health Organization HCV elimination targets.

Methods. Between October 2015 and May 2016, we performed a systematic HCV RNA–based screening among HIV-infected MSM participating in the Swiss HIV Cohort Study (SHCS). HCV antibodies were measured from all HCV RNA–positive samples.

Results. Of 4257 MSM recorded in the SHCS database, we screened 3722 (87%) by HCV polymerase chain reaction, and 177 (4.8%) harbored a replicating HCV infection. We identified 24 individuals (14%) with incident HCV infection; one-third of them had a negative HCV antibody result at the time of HCV RNA positivity. In a multivariable model, elevated liver enzyme values (odds ratio, 14.52; 95% confidence interval, 9.92–21.26), unprotected sex with occasional partners (2.01; 1.36–2.98), intravenous drug use (7.13; 4.36–11.64), noninjectable drug use (1.94; 1.3–2.88), and previous syphilis diagnosis (2.56; 1.74–3.76) were associated with HCV RNA positivity.

Conclusions. A systematic HCV RNA–based screening among HIV-infected MSM revealed a high number of potential transmitters. A substantial subpopulation of MSM had incident infection, one-third of whom had a negative HCV antibody test result at the time of the HCV RNA positivity. These data reveal that one-time RNA testing of a high-risk population for HCV RNA might identify more infected persons than routine testing for HCV antibodies and liver enzymes.

Keywords. men who have sex with men; hepatitis C virus; HCV; HCV screening; PCR.

Since the turn of the millennium, the incidence of hepatitis C virus (HCV) infections in human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) has been rising in industrialized nations [1–4]. In the Swiss HIV Cohort Study (SHCS), the proportion of MSM among patients with incident HCV infections has significantly increased, from 23% before 2006 to 85% thereafter [5, 6]. In contrast, we observed a very strong decline in the prevalence and incidence of HCV among persons who inject drugs (PWID) in Switzerland [6] because of successful harm reduction programs since the early 1990s [7–9].

During the last 3 decades, HCV prevention efforts have ignored MSM and focused on reducing HCV transmission among PWID [10]. With the epidemiological changes in HCV transmission that have been described, HIV-infected MSM are now the key population for targeted interventions [11]. In this context, early detection of potential HCV transmitters, followed by prompt HCV treatment initiation, could be reasonable strategies to interrupt the transmission chains [12, 13]. However, the best HCV screening strategy in high-risk populations is still a matter of debate [14–16]. To date, a polymerase chain reaction (PCR)–based HCV test is the reference standard for identifying individuals with replicating disease. However, the high costs of PCR-based HCV testing limit its

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implementation in clinical practice. Current guidelines recommend a HCV antibody test as the first screening test for HCV infection [17, 18]. In the case of suspected acute HCV infection (eg, unexpected elevation of liver enzyme levels), guidelines recommend HCV RNA or HCV core antigen testing as the initial evaluation [17, 18].

In the SHCS, HCV screening comprises an annual HCV antibody screening for MSM during routine clinical visits. However, using an HCV antibody test as a screening method is generating a considerable time lag, because it takes up to 6 months after HCV infection for HCV antibodies to be detected in the blood [19]. Although HCV seroconversion occurs in the majority of cases within 8 weeks when later-generation assays are used [20], a negative HCV antibody test does not reliably rule out incident HCV infection.

The Swiss HCVree Trial performed population-based systematic HCV RNA PCR testing among all MSM who participate in the SHCS and thereafter provided HCV treatment to all MSM detected with a replicating genotype 1 or 4 infection. This was in pursuit of a strategy with the primary goal of implementing an HCV elimination program at the population level. We concentrated our intervention on the MSM group, first because SHCS data suggest that HCV transmissions among PWID are almost absent [6, 21] and second because PWID with advanced liver diseases could be treated with standard of care direct-acting agents (DAAs) at the time of the study. Herein, we report on the screening period and discuss the implications of our findings for future HCV screening strategies.

METHODS

Swiss HCVree Trial and SHCS

The Swiss HCVree Trial is a prospective, multicenter, nationwide, interventional trial (NCT 02785666) within the SHCS consisting of 3 phases. Detailed information on the SHCS is provided in the Supplementary Material [22].

During screening period A, from 1 October 2015 to 30 June 2016, we performed systematic HCV RNA PCR–based testing among all MSM participating in the SHCS. Participants were screened at least once by HCV PCR during the 9-month screening period at one of the regular 6-monthly SHCS visits. The HCV RNA tests were paid for by Merck Sharp & Dohme. Liver enzyme (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels were measured at the same visit, reflecting standard-of-care SHCS procedures. In patients attending 3-monthly clinical visits, liver enzymes were measured more frequently, at 3-month intervals. HCV PCR was performed regardless of clinical suspicion for HCV infection or elevated liver enzyme levels. Detailed information on HCV testing and the costs of the HCV tests is provided in the Supplementary Material.

During period B, from 1 June 2016 to 28 February 2017, HCV treatment with the once-daily combination grazoprevir-elbasvir was provided to all MSM with replicating genotype 1 or 4 infection, regardless of fibrosis stage. The study drug was provided free of charge by Merck Sharp & Dohme in the context of this investigator-initiated trial. The treatment phase was accompanied by a risk behavioral intervention for MSM who reported unprotected sex with occasional partners, with the goal of preventing reinfection after successful HCV treatment. Individuals with genotype 2 or 3 infections were treated outside the study, using standard-of-care DAAs if reimbursement requirements were fulfilled.

During the rescreening period C, from 1 March to 30 November 2017, all MSM were retested with HCV PCR to assess preintervention and postintervention prevalences in the targeted population. Local ethics committees from all participating study sites approved the study, and written consent was obtained from all participants.

Definition of HCV Infection

Replicating HCV infection was defined as an HCV RNA result ≥100 IU/mL. We defined 3 categories for HCV infection: (1) *incident HCV infection* was defined as a negative HCV test (HCV RNA and/or anti-HCV immunoglobulin G) result documented in the SHCS database before 1 October 2015, with a positive HCV RNA result obtained thereafter; (2) *HCV reinfection* was defined as a positive anti-HCV immunoglobulin G test results but negative HCV RNA result documented in the SHCS database before October 1 2015, with a positive HCV RNA test obtained thereafter; and (3) *known HCV infection* was defined as a positive HCV test result documented in the SHCS database before 1 October 2015, with a positive HCV RNA result obtained thereafter.

Statistical Analysis

Statistical analysis was performed using Stata software, version 15 (StataCorp). Bivariate *P* values were calculated using Fisher exact test for categorical variables and Wilcoxon or Kruskal-Wallis test for continuous variables. Univariable and multivariable logistic regression analyses were performed with the outcome of replicating HCV infection and considering covariables that were significant in the bivariate analyses at $P < .05$.

RESULTS

Study Population and Number of Replicating HCV Infections

On 1 October 2015, a total of 9128 active individuals were recorded in the SHCS database (Figure 1). Of the 4257 MSM recorded, 3722 (87%) were screened with HCV RNA PCR. Reasons for a missed HCV RNA screen (n = 535) included dropout from the SHCS, living abroad, misclassification of MSM state in the SHCS database, death, or withdrawal of consent.

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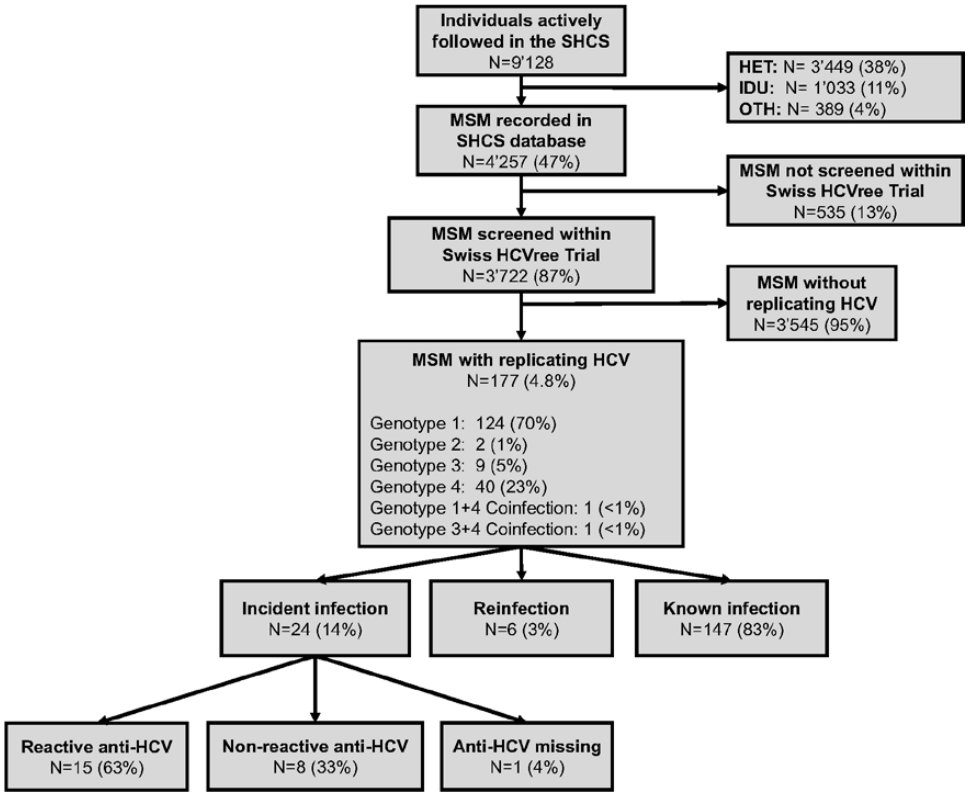

Figure 1. Flowchart of human immunodeficiency virus (HIV)–positive men who have sex with men (MSM) screened for the Swiss HCVree trial. Abbreviations: HCV, hepatitis C virus; HET, heterosexuals; IDU, intravenous drug users; SHCS, Swiss HIV Cohort Study.

Of the 3722 MSM who were screened during the study period, 177 (4.8%) harbored a replicating HCV infection. Five individuals had a HCV PCR result >12 IU/mL and <100 IU/mL, and 3 of them were retested with the Abbott RealTime HCV assay. Subsequent HCV PCR testing revealed a negative HCV PCR result in all individuals, so we thus considered the results at first testing as false-positive. For the remaining 2 individuals, subsequent PCR testing was not available. Genotype 1 was the most prevalent genotype (n = 124; 70%), followed by genotypes 4 (n = 40; 23%), 3 (n = 9; 5%), and 2 (n = 2; 1%). The baseline characteristics of all screened MSM stratified by replicating and nonreplicating HCV infection are shown in Table 1.

Risk Factors for Replicating HCV Infection

Risk factors for replicating HCV infection are shown in Table 1. In the multivariable analysis adjusted for all variables significantly associated with replicating HCV in Table 1, elevated liver enzyme values at the time of HCV RNA positivity (odds ratio, 14.52; 95% confidence interval, 9.92–21.26), unprotected sex with occasional partners (2.01; 1.36–2.98), intravenous drug use (7.13; 4.36–11.64), noninjectable drug use (1.94; 1.3–2.88), and previous syphilis diagnosis (2.56; 1.74–3.76) were positively correlated with HCV RNA positivity (Figure 2). The receiver operating characteristic curve of risk factors from the multivariable model was 0.86.

Type of HCV Infection, HCV Serological Status, and Liver Enzyme Levels

Of the 177 MSM with replicating HCV, 24 (14%) had an incident HCV infection and 6 (3%) were classified as having reinfection (Figure 1). The remaining 147 MSM with replicating HCV (83%) had known HCV infections. Of the 24 MSM with an incident HCV infection, 8 (33%) had a negative HCV antibody test result at the time of the positive HCV RNA screen. The characteristics of these 8 individuals are shown in Table 2. The potential delay in diagnosing HCV infection by performing standard-of-care annual HCV antibody testing was estimated by calculating the time (in days) from the first positive HCV RNA result to the time of the planned HCV serology 1 year after the last negative HCV serological result. Based on this approach, we calculated that detection of the HCV infection would have been delayed by a median of 197 days (range, 53–366 days). Fifty-four of the 177 MSM with replicating HCV infection (31%), and 4 of the 24 with incident HCV infection (17%) presented with normal liver enzyme levels at the time of the positive HCV RNA screen result. Of the 8 MSM with an incident HCV infection and a negative HCV antibody result at the time of the positive HCV RNA screen, 2 presented with normal liver enzyme values (Table 2).

Characteristics of Patients With Incident HCV Infection and Reinfection

Compared with MSM with a known HCV infection, those with an incident HCV infection were younger (39 vs 48 years;

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Table 1. Baseline Characteristics of 3722 Men Who Have Sex With Men Screened for Hepatitis C Virus (HCV) Infection by HCV RNA Polymerase Chain Reaction, Stratified by Replicating State

Characteristic	No. With Data	All Participants	Replicating HCV	Nonreplicating HCV	*P* Value
No. of patients (%)	3722	3722 (100)	177 (4.8)	3545 (95.2)	…
Age, median (IQR), y	3715	50 (42–56)	47 (41–54)	50 (42–56)	.007
Ethnicity, No. (%)	3711				
White		3360 (90.5)	159 (89.8)	3201 (90.6)	.34
Black		60 (1.62)	6 (3.4)	54 (1.5)	
Asian		135 (3.6)	7 (4.0)	128 (3.6)	
Hispanic		152 (4.1)	5 (2.8)	147 (4.2)	
Other/unknown		4 (0.1)	0 (0.0)	4 (0.1)	
HIV-related data					
Time since HIV diagnosis, median (IQR), y	3715	12 (7–20)	11 (7–20)	12 (7–20)	.95
Prior AIDS, No. (%)	3538	696 (18.7)	31 (17.5)	665 (18.8)	.38
HIV viral load <50 copies/mL, No. (%)	3445	3397 (94)	156 (92.3)	3241 (94.1)	.21
CD4 cell count, median (IQR), cells/μL	3640	630 (480–828)	629.5 (463–778.5)	630 (480–829.5)	.22
Liver-related data					
ALT, median (IQR), U/L	3236	29 (22–42)	74 (42–141)	29 (21–40)	<.001
AST, median (IQR), U/L	3208	26 (22–33)	51 (33–77)	26 (21.6–31.6)	<.001
AST or ALT >50 U/L, No. (%)	3061	584 (18.0)	123 (69.5)	461 (15.1)	<.001
History of hepatitis B infection, No. (%)	3288	1503 (43.6)	78 (50.2)	1425 (43.3)	.052
Other risk factors, No. (%)					
Condomless sex with occasional partners	3492	932 (25.4)	83 (47.4)	849 (24.3)	<.001
Condomless sex with stable partner	3520	1235(33.4)	54 (30.7)	1181 (33.6)	.24
Intravenous drug use	3532	202(5.4)	51 (29.0)	151 (4.3)	<.001
Noninjectable drug use	3532	1145(30.8)	106 (60.2)	1039 (29.4)	<.001
Previous syphilis diagnosis	3475	1512(41.5)	106 (65.4)	1406 (40.5)	<.001
Severe alcohol consumption	2970	725 (23.3)	30 (21.9)	695 (23.4)	.39

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

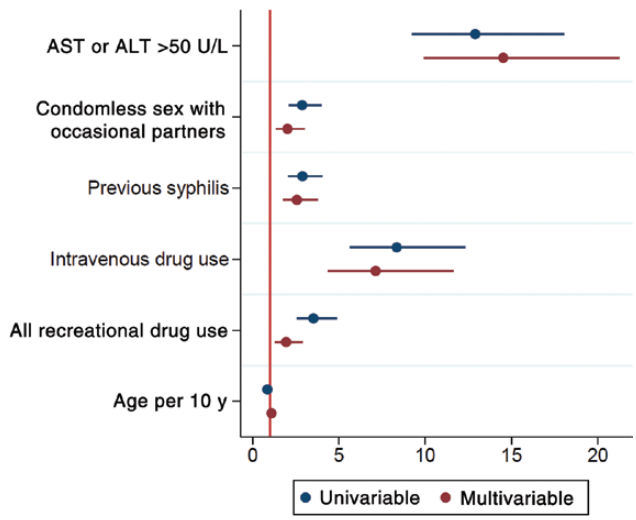

Figure 2. Univariable (*blue*) and multivariable (*red*) logistic regressions for factors associated with a positive hepatitis C virus RNA screening. Abbreviations: ALT, alanine aminotransferase; AST, aspartate, aminotransferase.

P < .001), had a more recent HIV infection diagnosis (6 vs 12 years; *P* < .001), and had higher ALT levels (125.5 vs 68 U/L; *P* = .009) (Table 3). For the incident infections, the median time from the last negative HCV serological result recorded in the SHCS database to the time of HCV RNA positivity was 381 days (interquartile range, 259–800 days).

DISCUSSION

In this nationwide, prospective, multicenter, interventional trial, we found that 177 of 3722 MSM from the SHCS had a replicating HCV, reflecting a prevalence of 5%. Most importantly, 14% of MSM with replicating HCV had an incident HCV infection and one-third of these patients presented with a nonreactive HCV antibody test at the time of the positive HCV RNA result.

Our finding that a substantial proportion of MSM with incident HCV infection had a negative HCV antibody result at the time of HCV RNA positivity highlights the importance of a screening approach based on a molecular test in the setting

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Table 2. Characteristics of 8 Patients With an Incident Hepatitis C Virus (HCV) Infection and a Negative HCV Antibody Test Result at the Time of Positive HCV RNA Result[a]

Subject	Genotype	Date of 1st Positive HCV RNA[b]	Date of Last Negative HCV Antibody Test[b]	AST at Time of Positive HCV RNA, U/L	ALT at Time of Positive HCV RNA, U/L	Calculated Potential Delay in HCV Diagnosis, d
1	1a	22/2/2016	10/10/2015	752	1013	231
2	4	17/11/2015	12/1/2015	29	33	56
3	1a	26/10/2015	8/9/2014	32	47	366
4	1a	22/2/2016	7/10/2015	40	69	228
5	1a	21/1/2016	17/4/2015	30	53	87
6	1a	11/12/2015	11/9/2015	39	62	275
7	1a	29/7/2016	29/9/2015	663	1106	53
8	1a	17/11/2015	24/8/2015	59	89	281

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus.

[a]The estimated delay in diagnosing HCV infection was calculated by assessing the time (in days) from the first positive HCV RNA test result to the recommended HCV antibody test 1 year after the last negative HCV antibody test result.

[b]Dates presented in date/month/year format.

of a population-based HCV elimination strategy. In June 2016, the World Health Organization launched its action plan, setting the goal of eliminating viral hepatitis as a major public health threat by 2030 [23]. Aiming at preventing sexual transmission of viral hepatitis, the action plan states that specific attention should be given to MSM with high-risk behavior. Recognizing the recently described epidemiological changes in HCV transmission among HIV-infected MSM in Switzerland, the Swiss HCVree Trial was established to identify MSM in the SHCS with replicating infection and to treat these MSM regardless of

Table 3. Comparison of Men Who Have Sex With Men With Replicating Hepatitis C Virus (HCV) Infection, Stratified by Incident Infection, Reinfection, or Known HCV Infection

Characteristic	No. With Data	Incident HCV Infection	Reinfection	Known HCV Infection	*P* Value
No. of patients (%)	177	24 (13.6)	6 (3.4)	147 (83.1)	…
Age, median (IQR), y	177	39.5 (32–47)	40.5 (37–41)	48 (42–55)	<.001
HIV-related data					
Time since HIV diagnosis, median (IQR), y	177	6 (4–9.)	6.5 (4–12)	12 (8–22)	<.001
Prior AIDS, No. (%)	177	6 (25.0)	0 (0.0)	25 (17.0)	.37
HIV viral load, <50 copies/mL, No. (%)	169	21 (91.3)	5 (83.3)	130 (92.9)	.42
CD4 cell count, median (IQR), cells/μL,	172	742.5 (448–816)	660.5 (496–856)	609.5 (460–734)	.57
CD4 cell count <200 cells/μL, No. (%)	172	3 (12.5)	0 (0.0)	1 (0.7)	.02
Liver-related data					
HCV genotype, No. (%)	177				
1a		20 (83.3)	2 (33.3)	88 (59.9)	.32
1b		0 (0.0)	1 (16.7)	13 (8.8)	
2		0 (0.0)	0 (0.0)	2 (1.4)	
3		0 (0.0)	0 (0.0)	9 (6.1)	
4		4 (16.7)	3 (50.0)	33 (22.5)	
1/4 Coinfection		0 (0.0)	0 (0.0)	2 (1.4)	
HCV RNA, median (IQR), log IU/mL)	177	5.78 (5.32–6.86)	5.06 (4.04–5.79)	6.00 (5.50–6.56)	.08
Anti-HCV positivity at screening, No. (%)	169	15 (62.5)	3 (50.0)	141 (95.9)	.000
Fibrosis stage at baseline (METAVIR score), No. (%)	163				
F0–F1		14 (70.0)	3 (75.0)	103 (74.1)	.68
F2		4 (20.0)	1 (25.0)	26 (18.7)	
F3		2 (10.0)	0 (0.0)	5 (3.6)	
F4		0 (0.0)	0 (0.0)	5 (3.6)	
ALT, median (IQR), U/L	177	125.5 (61.5–352.5)	188 (72–306)	68 (41–125)	.009
AST, U/L, median (IQR)	177	59 (39.5–141.5)	87 (46–141)	47 (33–71)	.04
AST or ALT >50 U/L, No. (%)	177	20 (83.3)	5 (83.3)	98 (66.7)	.23
Previous HCV treatment, No. (%)	174	0 (0.0)	31 (21.5)	1 (16.7)	.02

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

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reimbursement restrictions, with the goal of rapidly reducing the pool of potential transmitters.

The HCV prevalence of 5% assessed in our HIV-infected population is remarkably high. A study performed in 2010 in Zurich, Switzerland, found a HCV seroprevalence of 0.37% among 821 HIV-uninfected MSM, only 1 of whom harbored replicating virus [24]. For the HIV-infected MSM population in Switzerland, the point prevalence of replicating HCV has not been systematically determined so far. Wandeler et al [6, 25] assessed the number of HCV infections among HIV-infected MSM in the SHCS from 1998 to 2011 and found that 147 of 4629 MSM (3.2%) had a positive HCV serological result at the time of study entry. However, some of them had been treated in the meantime or experienced spontaneous clearance, and therefore these data do not reflect the current prevalence of replicating HCV infection. The unique setting of the SHCS combined with our systematic HCV RNA screening allowed us for the first time to determine exact HCV prevalence and incidence data in the HIV-infected Swiss MSM community.

With our systematic HCV RNA–based screening, we tested almost 4000 HIV-infected MSM for HCV. One of the key questions regarding such an approach is whether this truly reflects the population at risk or if HIV-uninfected MSM should also be included in a systematic HCV screening program. There is evidence from literature that the HCV epidemic is concentrated among HIV-infected MSM [4, 26]. However, a recent study from Amsterdam that tested high-risk HIV-uninfected MSM for HCV by HCV antibodies and HCV RNA found a similar HCV prevalence of 4.8% [27]. Given the heterogeneous risk profile of MSM for HCV, and the high costs of HCV RNA–based screening programs, a screening algorithm based on individual risk factors could be a reasonable strategy for the future.

A risk-based HCV RNA screening approach should be based on factors that are independently associated with a positive HCV RNA screen. Most of these risk factors we have found to be a proxy for high-risk transmission behavior and have been associated with a higher risk for HCV acquisition in previous studies [21, 28–31]. They can be easily assessed within a short time and could guide the clinician to opt for an HCV PCR test instead of the usual HCV antibody screening. That a risk factor–based screening approach might be useful in finding new HCV diagnoses has been previously shown in other settings, for example, among PWID.

In a study by Kim et al [32], newly incarcerated inmates were screened for acute HCV infection by using a simple screening questionnaire and an AST threshold >7 times the upper limit of normal. With this risk-based screening, the authors identified 1 case of acute HCV infection per 100 persons screened. However, in the setting of an AST-based screening approach, one must remember that the absence of liver enzyme elevation does not rule out an HCV infection; one-third of the MSM with a positive HCV RNA test result did not have elevated liver enzyme level in our study at the time of the positive screen. On the other hand, elevated liver enzyme levels should prompt physicians to perform an HCV RNA test in individuals at high risk for HCV acquisition. The fact that in our study 15% of the MSM with a negative HCV RNA result nevertheless had elevated liver enzyme levels—defined as an AST or ALT level >50 U/L—reflects the high burden of liver disease and other comorbid conditions in HIV-infected individuals and emphasizes the need for a careful clinical assessment of elevated liver enzyme levels in this patient population [33]. The proportion of HCV RNA–negative MSM with elevated liver enzyme levels would even increase to 50% with an ALT cutoff of >30 U/L.

Our systematic HCV RNA–based screening approach identified a substantial proportion of MSM with an incident HCV infection. Remarkably, in our study one-third of patients with an incident HCV infection had a negative HCV antibody test result despite HCV replication. We calculated a median delay of 197 days (range, 53–366 days) in the diagnosis of incident HCV infection when following the SHCS standard-of-care annual HCV antibody testing. In the context of an elimination program, this delay could be relevant, because a timely diagnosis without gaps is paramount to following the principle of "treatment as prevention." The impact of this delay also depends on the fraction of transmission events during early infection phases. Although this is not known for HCV, detailed analyses of HIV suggest that early infection phases may play a crucial role for transmission and thus also for elimination [34].

One can argue that all but 2 of the MSM with an incident HCV infection would have been identified combining HCV serology as the initial screen with subsequent HCV RNA testing in case of a negative serological result with elevated liver enzyme levels. However, this strategy would also generate a high number of PCR tests because of the high proportion of HIV-infected individuals with elevated liver enzymes. In addition, it would be logistically challenging, because the patient had to attend the clinic twice for the subsequent HCV PCR test. Because the cost of HCV PCR in our elimination study were similar to that of a commercially available HCV antibody test, a stepwise testing approach would have generated even higher costs than systematic PCR-based screening. Such low prices for HCV PCR are negotiable if big test volumes are used for population wide programs for example, for elimination programs.

Our study had several strengths. The study population is very representative of the HIV-infected MSM community living in Switzerland; models estimate that about 75% of all HIV-infected MSM living in Switzerland participate in the SHCS [35]. Because we used a very sensitive PCR assay for HCV screening, a negative test result could reliably rule out replicating HCV in the tested individual. As a limitation, we cannot rule out the possibility that we missed an HCV infection that occurred after the negative screening and HCV transmission events, which affected non-SHCS participants. In addition, because the

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natural history of HCV infection can be characterized by HCV RNA negativity and subsequent clearance but also by recurrence of viremia after alleged clearance [36], we might missed such cases. However, given that all MSM were rescreened during period C, this probability is rather low. Another limitation is that our systematic HCV screening approach leads to an unnecessary screening of MSM with a very low risk for HCV and was associated with substantial costs, but this strategy was essential to identify risk factors. Finally, contamination of specimens or borderline results may have led to misinterpretation of the test results, leaving the participants with some unease.

In conclusion, our study findings have several important implications for reaching the World Health Organization targets of a 90% reduction in new HCV cases by 2030. First, in the context of a HCV elimination strategy, HCV RNA–based screening should be considered in sexually active MSM, particularly when they report the above-mentioned risk factors. The strategy of using HCV PCR to screen high-risk MSM with signs of acute HCV infection is also recommended by international guidelines [37]. This is because delayed diagnosis and therapy substantially increase the time individuals spend with replicating HCV infection and therefore the probability of their transmitting the infection to other sex partners. A test for HCV core antigen as a surrogate marker of HCV replication can be performed when HCV RNA tests are not available or not affordable [17]. Second, we recommend PCR-based screening in patients with successfully treated or self-cleared HCV infections. This is for timely identification of reinfection and/or relapse. Third, batch-wise HCV RNA screening is encouraged in order to lower costs. Finally, consultations should be used to promote safer sex practices, because suppressive antiretroviral therapy does not replace condoms for protection from HCV and other sexually transmitted infections in general.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. L. B., A. R., J. B., and J. S. F. designed the study. D. L. B., B. H., C. G., M. F., M. S., A. C., C. B., P. S., J. D., M. R., E. B., and J. B. acquired the data. R. K. and K. K. performed statistical analysis. D. L. B., J. B., and J. S. F. supervised the study. D. L. B. wrote the first draft of the manuscript. All investigators contributed to data collection and interpretation, reviewed drafts of the manuscript, and approved the final manuscript.

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