A treatment as prevention trial to eliminate hepatitis C among men who have sex with men living with HIV in the Swiss HIV Cohort Study

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Summary:

We systematically assessed the feasibility of a test, treat and cure hepatitis C (HCV) micro-elimination program among men who have sex with men living with HIV. Our elimination program led to a 77% decrease in the HCV incidence rate.

Abstract

Background: In 2016, the World Health Organization (WHO) introduced global targets for the elimination of hepatitis C (HCV) by 2030. We conducted a nationwide HCV micro-elimination program among men who have sex with men (MSM) living with HIV from the Swiss HIV Cohort Study (SHCS) to test whether the WHO goals are achievable in this population.

Methods: During phase A (10/2015-06/2016), we performed a population-based and systematic screening for HCV-RNA among MSM from the SHCS. During phase B (06/2016-02/2017) we offered treatment with HCV direct-acting agents (DAAs) to MSM identified with a replicating HCV infection. During phase C (03/2017-11/2017), we offered re-screen to all MSM for HCV-RNA and initiated DAA treatment in MSM with replicating infections (Clinicaltrials.gov NCT02785666).

Findings: We screened 3'715/4'640 (80%) MSM and identified 177 with replicating HCV infections (4.8%); 150 (85%) of which started DAA treatment and 149 (99.3%) were cured. We re-screened 2'930/3'538 (83%) MSM with a prior negative HCV-RNA and identified 13 (0.4%) with a new HCV infection. At the end of the micro-elimination program, 176/190 MSM (93%) were cured, and the HCV incidence rate declined from 0.53 per 100 patient-years (95% confidence interval [CI] 0.35, 0.83) prior to the intervention to 0.12 (CI 0.03, 0.49) by the end of 2019.

Interpretation: A systematic and population-based HCV micro-elimination program among MSM living with HIV was feasible and resulted in a strong decline in HCV incidence and prevalence. Our study can serve as a model for other countries aiming to achieve the WHO HCV elimination targets.

Introduction

Viral hepatitis is now a leading cause of death among people suffering from communicable diseases worldwide, surpassing human immunodeficiency virus (HIV), tuberculosis and malaria[1]. Among cases of viral hepatitis, hepatitis C (HCV) infection is the leading cause of liver-related mortality[2]. As a response to this global epidemic, in 2016 the World Health Organization (WHO) released its first global strategy on viral hepatitis by calling for the elimination of HCV[3]. The WHO targets for HCV in 2020 and 2030 are to achieve a 30% and 80% reduction of new HCV infections, and a 10% and a 65% reduction in HCV-related deaths, respectively[3]. However, the prospect of HCV elimination is extremely challenging because of the scale, complexity and cost of elimination strategies[4,5]. Therefore, one pragmatic approach is to break down elimination goals into smaller goals for population segments with specific characteristics, referred to as micro-elimination[6].

The WHO action plan states that micro-elimination efforts should include people living with HIV and specific attention should be paid to men who have sex with men (MSM) practicing risky sexual behaviors. Within this population, HCV infection incidence is particularly high and HCV epidemics among HIV-seropositive MSM have been observed in recent years[7,8]. As an example, in the Swiss HIV Cohort Study (SHCS) from 2006 to 2012, 74% of incident HCV infections were identified in MSM, whereas the incidence rate dropped in people who inject drugs (PWID) and remained stable in heterosexuals[8].

Recognizing this new HCV epidemic within the SHCS, we conducted the Swiss HCVree Trial with the goal of implementing a population-based systematic HCV micro-elimination program among MSM living with HIV within the SHCS[9,10]. We concentrated on HIV-diagnosed MSM, as data show that the HCV transmission in Switzerland occurred mainly amongst this group[8,11]. The aim of our study was to test whether WHO HCV elimination targets are achievable in clinical practice among MSM living with HIV.

Methods

Swiss HCVree Trial and Swiss HIV Cohort Study

The Swiss HCVree Trial was designed as a nationwide prospective, multi-center, interventional trial (NCT 02785666) in the framework of the SHCS[12]. In the SHCS, sexually active MSM are yearly screened for HCV antibodies. In all other MSM, HCV antibody testing is done every two years.

The Swiss HCVree Trial consisted of three phases: During phase A (10/2015 - 06/2016), all SHCS physicians and study nurses were asked to test MSM from the SHCS for HCV-RNA[9]. During phase B (06/2016 – 02/2017), direct acting antiviral agent (DAAs) treatment was provided to all MSM with a replicating infection regardless of fibrosis stage[10]. Details about the study-treatment are provided in the supplementary material. During phase C (03/2017 – 11/2017), SHCS physicians and study nurses were asked to test again all MSM for HCV-RNA.

Local ethical committees of all participating study sites approved the study and written consent was obtained from all participants.

Study population and study measurements

All MSM enrolled in the SHCS were eligible to participate in the study. MSM were defined as male participants reporting a homosexual or bi-sexual HIV-transmission mode and/or a sexual preference at SHCS enrolment. MSM attending a clinical visit during the phases A and C were systematically screened for HCV-RNA. HCV-RNA testing was performed using the Abbott RealTime HCV with a limit of quantification of 12 IU/mL. HCV-antibodies were measured from all HCV-RNA positive samples. Detailed information on the phase A and B are published elsewhere[9,10].

Retrospective HCV testing Swiss HIV Cohort Study database

After completion of the trial, we retrospectively retrieved information on HCV testing (i.e., recorded HCV-antibodies and/or HCV-RNA results) and DAA treatment of MSM not screened during the phases A and C from the SHCS database. This allowed us to improve the representativeness of the estimates for HCV prevalence and incidence at the population level. Detailed information is provided in the supplementary material.

Definition of HCV infection, type of HCV infection and HCV incidence

Replicating HCV infection was defined as an HCV-RNA result ≥100 IE/mL[9]. The definition of different types of HCV infections is provided in the supplementary material. The incidence for new HCV infections expressed in 100 patient-years (py) was calculated by using the midpoint of the last negative and the first positive HCV-RNA

and/or anti-HCV-IgG test whichever came first, and the incidence of HCV re-infection by using the midpoint of the last negative HCV-RNA and the first positive HCV-RNA test.

Phylogenetic analyses of incident HCV infections

Incident genotype 1a HCV infections identified during phase C were sequenced using Illumina technology. Maximum-likelihood phylogenetic trees, containing a fragment of the NB5B region of these and other circulating strains, were built. The strains were retrieved from national and international databases [13].

Statistical analysis

Statistical analysis was performed using Stata version 15.1 (StataCorp, College Station, Texas, USA). Bivariate p-values were calculated using Fisher`s exact test for categorical variables and Wilcoxon test or Kruskal-Wallis test for continuous variables. The incidence rate was calculated by tabulating the number of incident infections for patients screened during both phases A and C, with the time-at-risk calculated as between the dates of blood sampling in phases A and C. 95% Confidence Intervals (CI) were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameters. Statistical significance was set at $p \leq 0.05$.

Results

Screening phase A

Prior to phase A (per June 1st 2015), 9'128 individuals with ongoing follow-up were recorded in the SHCS database, of which 4'640 (51%) were MSM (Figure 1, Panel A). During phase A, we screened 3'715 (80%) MSM for HCV-RNA and identified 177 with a replicating HCV infection, thus suggesting a phase A prevalence of 4.8%. The reasons for a missed HCV screening are published elsewhere[9].. Of those 177 MSM with a positive HCV-RNA screen, 147 (83%) were prevalent HCV infections already known to the investigators prior to the phase A (Figure 2). The remaining 30 (17%) HCV infections were not previously diagnosed: 24 (80%) were incident primary HCV infections and six (20%) were incident HCV re-infections (Figure 2). Eight patients with an incident primary HCV infection (27%) had a negative HCV antibody test at the time of the positive HCV-RNA screen[9]. Information on HCV test frequency amongst the MSM in the SHCS prior to phase A as well on the incident HCV infection date is provided in the supplementary.

The baseline characteristics of MSM included in the Swiss HCVree Trial stratified by the different study phases and the HCV screening state are depicted in Table 1. Factors significantly associated with a missed HCV screen during either phase A or C included older age, not reporting intravenous drug use, and being followed by a SHCS private physician (Table 1). For those MSM not screened during phase A, the HCV antibody status was retrospectively retrieved from the SHCS database for 919 (99%) of the 926 individuals. Of those 919 MSM, 861 (94%) had a negative HCV antibody test recorded in the SHCS database during their regular SHCS follow-up (Figure 1, Panel B). However, 58 MSM (6%) had a positive HCV antibody test: 33 (57%) with an undetectable HCV-RNA, 24 (41%) with a detectable HCV-RNA, and 1 (2%) without information about the HCV-RNA.

Overall 201 out of 4'640 MSM had a replicating HCV infection, thus suggesting an overall prevalence of 4.3%. Hundred-seventy-seven MSM with a replicating HCV infection were identified during screening phase A and 24 by retrieving the samples of participants with missing HCV screening from the SHCS repository.

Treatment phase B

During the treatment phase B, 150 out of the 177 patients (85%) with a replicating HCV infection were treated with DAAs from which 149 (99.3%) achieved SVR 12[10]. Of the remaining 27 patients, three patients showed a spontaneous clearance of the infection and one patient died of an opioid overdose unrelated to his HIV-HCV infection. Twenty-three out of 177 MSM (7%) with a replicating infection remained untreated at the end of phase B (Figure 2, Panel A). The reasons for not being treated where the physician's decision to postpone treatment (n=8) and the patient refusing DAA treatment (n=14)[10]. One patient was lost to follow-up. Of the 24 MSM not screened during phase A but with a replicating HCV infection according to the retrospective assessment of the SHCS database, 15 (65%) were treated outside of the Swiss HCVree Trial and achieved SVR 12. No information was available on the remaining nine individuals. The treatment phase was accompanied by a newly developed behavioral intervention tailored towards HCV risk reduction. Details about the behavioral intervention was published elsewhere[10,14].

Re-screening phase C

During phase C, we re-screened 2'930 (83%) out of the 3'538 MSM who had a negative HCV-RNA screening result during phase A (Figure 1, Panel A). Of those, 13 (0.4%) had a positive HCV-RNA screening result and therefore were classified as incident primary HCV infection (Figure 2). The remaining 2'917 MSM (99.6%) had

a negative HCV-RNA screening result. All of the 177 MSM with a replicating HCV infection initially identified during phase A were also rescreened: 154 (87%) had a negative HCV-RNA and 23 had a positive HCV-RNA (Figure 2). These 23 reflect the group of the patients not treated during phase B for the reasons stated above.

Of the 3'538 MSM screened during phase A, 608 (17%) were not re-screened during phase C (Figure 1, Panel A). Of these, between phases A and C, 138 MSM (23%) had left the SHCS for various reasons: 37 left the country, 34 died, 10 discontinued the SHCS, 12 changed to a non-SHCS physician, 38 were lost to follow-up and for seven MSM there was no information available. For the remaining 470 MSM not screened during phase C, we were able to retrospectively retrieve the HCV antibody status from the SHCS database for 466 MSM (Figure 1, Panel B). Of these 466 MSM, 430 (92%) had a negative HCV antibody test recorded in the SHCS database whereas 36 MSM (8%) had a positive HCV antibody test: 33 (92%) with a negative HCV-RNA and 3 (8%) with a positive HCV-RNA. For these three infections, a prior positive HCVHCV test was recorded in the SHCS database and therefore they were classified as prevalent HCV infections. No information was available on the remaining four individuals. In sum, we identified 180 MSM with a replicating HCV infection between phases A to C.

Overall, phase C identified 13 MSM with an incident primary HCV infection, 23 MSM with a prevalent infection because they were not treated during phase B, and 3 MSM which were identified with a prevalent infection by the retrospective assessment of the SHCS database. Of those 39 MSM, 25 (64%) started DAA treatment during phase C and all achieved SVR 12. At the end of phase C, only 14 out of 180 MSM (7%) identified with a replicating infection through the elimination program remained untreated, suggesting a post-intervention prevalence of 0.4%.

HCV incidence

Overall, 34'318 years of observation amongst 5'260 MSM with an active follow-up since 2010 were analyzed. The mean follow-up time per MSM was 6.52 years (IQR: 3.75-9.3). The number of new HCV infections and re-infections is depicted in Figure 3: Between 2014 and 2019, we observed a decline in the incidence rate of incident primary HCV infections from 0.49/100 py (95% confidence intervals [CI]: 0.3, 0.78) in 2014 to 0.12/100 py (95% CI: 0.03, 0.5) by end of October 2019 (data from November to December not yet available). Similarly, the incidence rate of HCV re-infections declined from 2.86/100 py (95% CI: 0.71, 11.4) in 2014 to zero by end of October 2019. Prior to phase A (2014), the combined HCV incidence was 0.53/100 py (95% CI:

0.34, 0.83) and declined to 0.12/100 py (95% CI: 0.03, 0.48) by end of October 2019, reflecting a 77% decrease in new infections.

Phylogenetic analysis of incident HCV infections

In order to classify incident HCV infections as either domestically acquired or abroad, we sequenced six out of the eight incident genotype 1a infections identified during phase C. In two cases, the strains couldn't be sequenced because of technical reasons. We restricted the analysis to genotype 1a infections because this is the most prevalent genotype among MSM living with HIV in the Western world. Of the six sequences, two were located in clusters consisting of predominantly Swiss and German sequences. The remaining four sequences were classified as corresponding to international transmissions.

Discussion

We conducted the Swiss HCVree Trial to test the concept of HCV micro-elimination among MSM living with HIV in Switzerland. Our elimination program led to a 57% and 84% decrease of incident and prevalent HCV infections, respectively, within two years (Figure 2). Similarly, we observed a 77% decline in the HCV incidence rate (Figure 3). However, the effect of our elimination program on the incidence rate was delayed with the most pronounced decline observed in 2019. The overall prevalence of replicating HCV infections dropped from 4.3% prior to the intervention to 0.4% after the intervention. With this effort, we outperformed the WHO HCV elimination goals for 2020 amongst this sub-population and laid the groundwork to achieve the elimination goals for 2030. Our study can serve as a model for other countries, which are aiming to achieve the WHO elimination targets.

Our HCV elimination program is the first one who systematically assessed the feasibility of a test, treat, and cure HCV micro-elimination program among MSM living with HIV. Novel to other studies, we systematically screened MSM for HCV-RNA to detect HCV infections at the earliest stage and repeated RNA-based screening after universal DAA treatment among those identified with a replicating infection. We showed that this approach was feasible and resulted in a more than fifty percent decline in the incidence rate of HCV infections by end of 2018 and a ten-fold decrease in the point prevalence of replicating HCV infections. Other successful HCV micro-elimination programs focussing on people living with HIV co-infected with HCV have been recently reported from Australia, the Netherlands and the United Kingdom[15-18]. In the Australia CEASE study, following universal access to HCV DAA treatment, the HCV viremic prevalence dropped from 82% in

2014 to 8% in 2018[17]. In a retrospective cohort study conducted at three London HIV clinics, a 74% reduction in incident primary infections occurred in MSM living with HIV, coinciding with wider access to DAA-based therapy across London[18]. Finally. in the Dutch Athena cohort the incidence of new HCV infections decreased by >50% after unrestricted access to HCV treatment[16]. This study was not prospectively planned as an elimination program and did not use a systematic test and treat approach. These examples show that an increase in diagnosis and treatment rates can lead to substantial achievements towards HCV elimination.

Our study shows the potential but also the challenges of HCV elimination programs: Despite massive efforts within a representative cohort in a resource-rich country, we were still unable to screen a considerable number of MSM in both phases A and C. This is because some physicians decided not to screen their patients within the trial. A reason for that might be the physician's assumption of low-risk level for HCV infection in their patients. This hypothesis is supported by the fact that more than 94% of MSM with a missed HCV screening had a negative HCV test recorded in the SHCS database following the trial. The background SHCS database with its high-quality data and systematic collection of clinical parameters allowed us to retrieve these data, test stored samples retrospectively and to close the gap of missing information. Hence, the implementation and evaluation of a HCV elimination programs without having a comprehensive background cohort should be considered with caution.

Our study is unique in regard to its systematic approach with a pre- and post-interventional HCV-RNA-based screening coupled with a tight treatment program. Another strength is that we offered HCV-RNA based screening to all MSM living with HIV within the SHCS. As shown in our study, one third of patients with an incident HCV infection had a negative HCV antibody test despite HCV replication[19]. We calculated a median delay of 197 days in the diagnosis of incident HCV infection when following the SHCS standard-of-care annual HCV antibody testing[9]. In the context of an elimination program, such a delay could be relevant because a timely diagnosis and, most importantly, immediate treatment initiation is crucial to avoid new HCV transmission to partners[20-22]

Although we did our best to prevent new HCV infections during the trial, we still identified incident infections after the intervention. For a small number of incident infections we were able to perform phylogenetic analyses, indicating an international transmission network as the source in most cases. With this in mind, HCV elimination programs will probably fail without established systematic re-screening if such a large fraction of infections is acquired abroad[20]. Therefore, a concerted international effort will be needed in order to eliminate

this epidemic in the long run. In addition, other public health strategies such as harm reduction measures for MSM who inject drugs

A limitation - but on the same time also a strength of our program - is that our intervention was limited to MSM living with HIV from the SHCS. With this approach, the generalizability of our findings to other risk groups is limited and HCV infections occurring outside of the SHCS were missed. However, we estimate that 84% of all MSM living with HIV in Switzerland are followed in the SHCS[23], hus, our study population is highly representative and includes the key population regarding the new HCV epidemic in a real-life setting. In addition, available data clearly suggest that the HCV transmission in Switzerland is concentrated within MSM living with HIV[11]. This may change in the future because recent studies report the spread of HCV from HIV-seropositive to high-risk HIV-seronegative MSM[24]. HCV transmissions among other risk groups, in particular among PWID, have almost stopped[8,11,25]. Finally, a possible limitation is that the incidence analysis is based on rather small numbers; hence, this does need to be interpreted with caution.

In conclusion, our results demonstrate the feasibility of a comprehensive systematic test, treat and cure HCV micro-elimination program among MSM living with HIV. Our approach could be proposed as a model to reach the WHO targets towards HCV micro-elimination in a setting with necessary resources. The fact that a substantial part of incident HCV infections occurred within international transmission networks shows that phylogenetic analysis is key to understand the epidemic. Likewise, it emphasizes the need for cross-international efforts to reach the WHO elimination goals. Finally, HCV-RNA based screening with timely diagnosis and treatment initiation is crucial among high-risk MSM to reduce onward transmission and to contain the HCV epidemic in the long-run [22]. Because if omitted, the spread of HCV in Switzerland will take off again[26].

NOTES

Author's contribution statement

The study was designed by DLB, AR, HFG, and JSF. Data acquisition was done by DLB, BH, CG, PK, CS, LS, AC, MF, MS, CB, PS, MR, JD, EB, DN, JB, AR, HG and JSF. Statistical analysis was performed by BL, HN and RDK. DLB and JSF supervised the study. DLB wrote the first draft of the manuscript. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

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The members of the Swiss HIV Cohort Study are: Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L,

Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C, Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

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Tables:

Table 1: Baseline characteristics of patients included in the Swiss HCVree Trial stratified by the different study phases and the HCV screening state.

	Phase A: Unscreened	**Phase A: Screened, Negative**	**Phase A: Screened, Positive**		**Phase C: Unscreened**	**Phase C: Screened, Negative**	**Phase C: Screened, Positive**	
	N = 925	**N = 3538**	**N = 177**		**N = 608**	**N = 3071**	**N = 36**	
Age Median [IQR]	49 [39-56]	49 [42-56]	47 [40-54]	*P value = 0.007*[a]	50 [42-57]	51 [43-57]	50 [45-53]	*P value = 0.509*[a]
Ethnicity								
White	813 (87.9)	3201(90.5)	160 (90.4)	*P value = 0.162*[b]	542 (89.1)	2728(88.8)	31 (86.1)	*P value = 0.354*[b]
Black	24 (2.6)	54 (1.5)	6 (3.4)		15 (2.5)	44 (1.4)	1 (2.8)	
Asian	60 (6.5)	148 (4.2)	4 (2.3)		32 (5.3)	118 (3.8)	2 (5.6)	
Latino	24 (2.6)	128 (3.6)	7 (4.0)		16 (2.6)	117 (3.8)	2 (5.6)	

Ever on ART								
Yes	911 (98.5)	3518 (99.4)	176 (99.4)	*P value =*	602 (99.0)	3056(99.5)	36 (100.0)	*P value =*
No	14 (1.5)	20 (0.6)	1 (0.6)	*1.000*[b]	6 (1.0)	15 (0.5)	0 (0)	*1.000*[b]
Ever reported intravenous Drug Use								
Yes	12 (1.3)	34 (1.0)	24 (13.6)	*P value*	23 (3.9)	109 (3.5)	11 (30.6)	*P value*
No	913 (98.7)	3503 (99.0)	153 (86.4)	*<0.001*[b]	584 (96.1)	2962 (96.5)	25 (69.4)	*<0.001*[b]
SHCS center								
Tertiary hospital	397 (42.9)	2113 (59.7)	88 (49.7)	*P value <*	308 (50.7)	1869 (60.9)	24 (66.7)	*P value =*
Non-tertiary hospital	100 (10.8)	189 (5.3)	22 (12.4)	*0.001*[b]	38 (6.3)	172 (5.6)	1 (2.8)	*0.871*[b]
Private physicians	316 (34.2)	855 (24.2)	50 (28.2)		181 (29.8)	716 (23.3)	8 (22.2)	
CD4 Nadir Median[IQR]	322 [194-569]	292 [177-478]	295 [193-509]	*P value = 0.398*[a]	300 [179-508]	291 [178-480]	335 [209-616]	*P value = 0.723*[b]

Prior AIDS diagnosis	137 (14.8%)	654 (18.5%)	30 (16.9%)	*P value = 0.678*[c]	127 (20.9%)	566 (18.4%)	7 (19.4%)	*P value = 0.353*[a]
CD4 at Baseline Median[IQR]	607 [463-782]	628 [476-824]	622 [450-773]	*P value = 0.178*[a]	632 [472-823]	66 [510-854]	654 [526-826]	*P value = 1.000*[c]
HIV RNA at baseline < 50 copies/mL	736 (87.2%)	3298 (93.6%)	156 (91.8%)	*P value = 0.336*[b]	566 (93.2%)	2984 (97.2%)	32 (88.9%)	*P value = 0.658*[a]
HIV subtype								
Subtype B	600 (84.5%)	2632(89.3%)	130 (90.1%)	*P value =*	414 (84.5%)	2323(90.2%)	28 (84.8%)	*P value =*
Other subtypes	110 (15.5%)	316 (10.7%)	13 (8.9%)	*0.676*[b]	76 (15.5%)	252 (9.8%)	5 (15.2%	*0.015*[b]

a. P value of Fisher Test between unscreened and screened populations

b. P value of Chi-squared Test between unscreened and screened populations

Figures

Figure 1:

Panel A: Study Flow-chart of the Swiss HCVree Trial. The dashed blue line subdivides the trial phase A from C. MSM from the Swiss HIV Cohort Study (SHCS) were systematically screened for HCV-RNA in both trial phases A and C. For MSM not screened during phase A (n= 925) and C (n= 608) data were retrospectively retrieved from the SHCS database as depicted in Panel B.

Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; SHCS: Swiss HIV Cohort Study; MSM: men who have sex with men

Panel B: Information from the Swiss HIV Cohort Study (SHCS) database for MSM with a missed HCV screening during the phases A and C**.** For 925 and 608 MSM not screened during phase A and C, respectively, data about the HCV serostatus and HCV-RNA were retrospectively retrieved from the SHCS database. The dashed blue line subdivides the trial phase A from C.

Abbreviations: HCV: hepatitis C virus; RNA: ribonucleic acid; Ab: antibody; SHCS: Swiss HIV Cohort Study; MSM: men who have sex with men

Figure 2: Prevalent and incident replicating hepatitis C virus (HCV) infections stratified by the trial phases A and C. Incident infections include incident primary HCV infections (N=24) and incident HCVre-infections (N=6).

Abbreviations: HCV: hepatitis C virus

Figure 3: Incidence rate of hepatitis C virus (HCV) infection stratified by year and by trial phase A to C. The three trial phases took place from October 2015 to June 2016 (phase A), June 2016 to February 2017 (phase B) and March 2017 to November 2017 (phase C). Universal access to direct acting HCV agents was available in Switzerland from October 2017. The dark circles indicate the incidence rate per 100 patient-years of new HCV infections with the corresponding 95% confidence intervals, whereas the open circles indicate the incidence rate per 100 patient-years of re-infections with the corresponding 95% confidence intervals. For 2019, data were

available for the first ten months until end of October 2019. **Panel A:** Primary HCV infections. **Panel B:** HCV re-infection. **Panel C:** Primary HCV infections and HCV re-infections combined.

Figure 1A

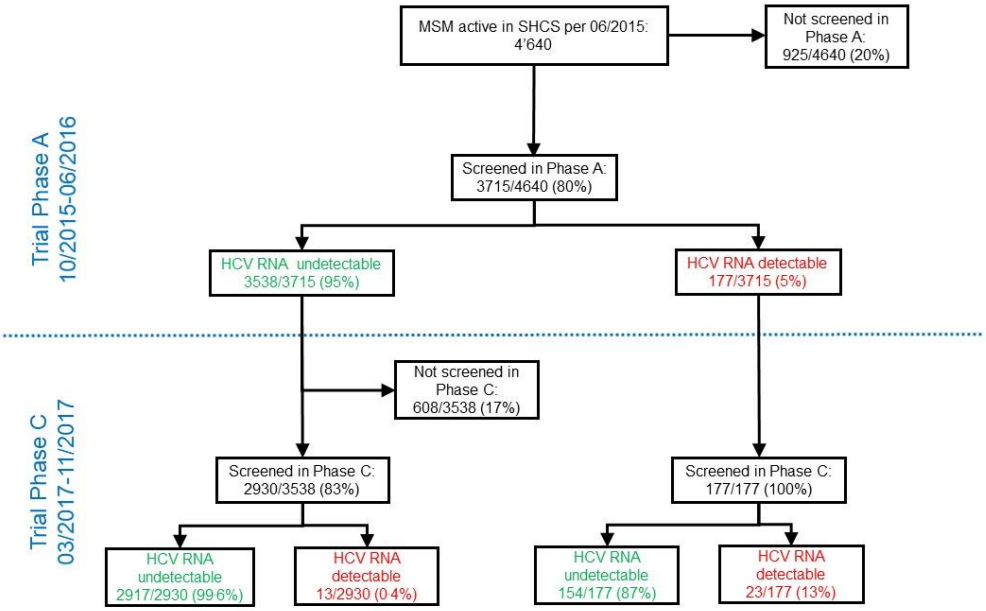

Figure 1B

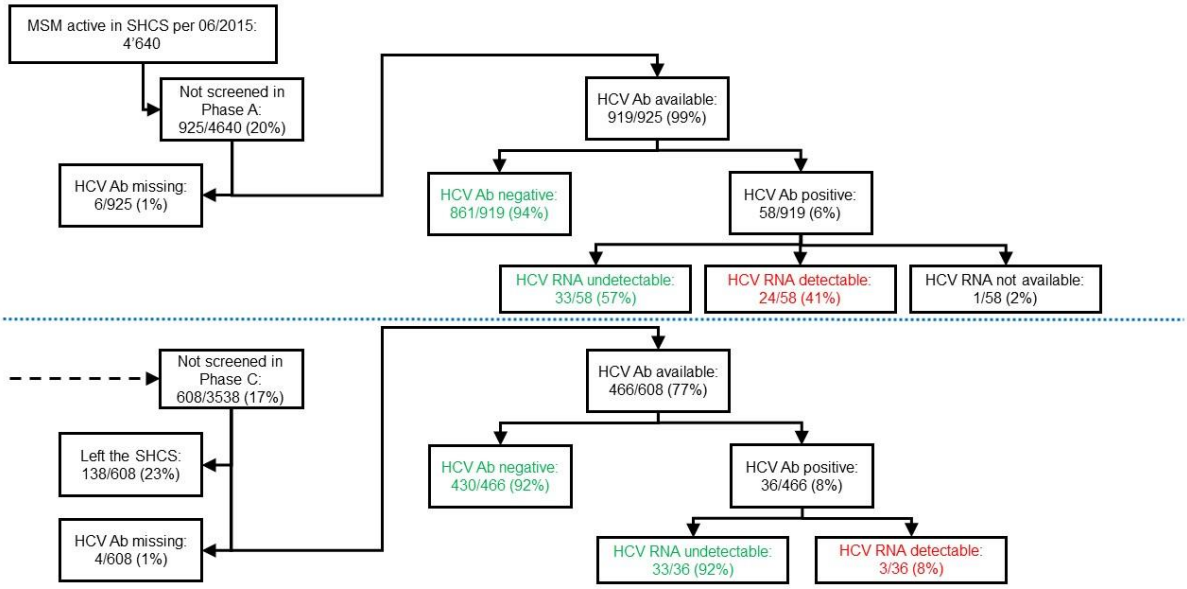

Figure 2

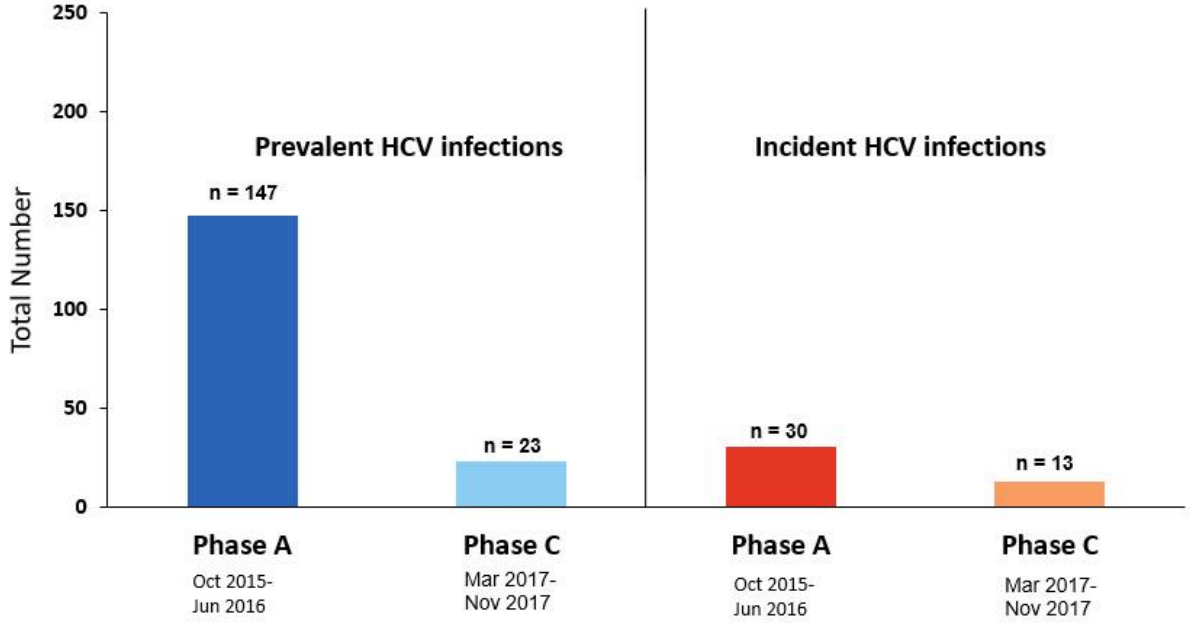

Figure 3