Sustained effect on hepatitis C elimination among men who have sex with men in the Swiss HIV Cohort Study: A systematic re-screening for hepatitis C RNA two years following a nation-wide elimination program

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Summary: A systematic hepatitis C RNA-based screening among men-who-have-sex-with-men-living with HIV conducted two years after the Swiss HCVree Trial revealed a sustained effect and further decline of the prevalence and incidence of replicating hepatitis C infection.

Short Title: HCVree Post Screening

Abstract

Introduction

The Swiss HCVree Trial (NCT 02785666) was conducted in 2015-2017 with the goal of implementing a population-based systematic hepatitis C (HCV) micro-elimination program among men who have sex with men (MSM) living with HIV enrolled in the Swiss HIV Cohort Study (SHCS). The trial led to a 91% and 77% decline of HCV prevalence and incidence, respectively. The long-term effect of this HCV micro-elimination program is yet to be explored.

Methods

All MSM enrolled in the SHCS were screened for HCV RNA using stored plasma samples obtained in 2019, termed "Swiss HCVree Post" screen. The incidence of HCV infection over time was assessed using additional information on HCV testing routinely collected in the SHCS. Characteristics of participants with replicating HCV infection were analyzed.

Results

The point-prevalence of "Swiss HCVree Post" (N = 4641) was 0.6%, reflecting a decline of 48% compared to the end of the Swiss HCVree Trial where the prevalence was 1.2%. Further, the incidence of HCV among MSM in the SHCS declined from 0.31/100 person-years (py) (95%-confidence interval (CI) = [0.17,0.55]) in 2017 to 0.19/100 py (95%-CI = [0.09,0.39]) in 2019.

Conclusion

A systematic HCV RNA-based screening among MSM living with HIV conducted two years after the Swiss HCVree Trial revealed a sustained effect and further decline of the prevalence and incidence of replicating HCV infection. This indicates that the Swiss HCVree Trial was successful in curbing the HCV epidemic among MSM living with HIV in Switzerland.

Introduction

In May 2016, the World Health Organization (WHO) adopted the first *Global health sector strategy on viral hepatitis, 2016-2021*, a strategy aiming for elimination of viral hepatitis as a public health treat by 2030. The main goals of this strategy are the reduction of new viral hepatitis infections by 90% and the reduction of viral-hepatitis-related deaths by 65% by 2030 (1). The WHO strategy includes several agenda points towards HCV elimination, most importantly improving the cascade of care by scaling up diagnosis and treatment to prevent further transmissions.

To reach this overarching goal, so-called micro-elimination interventions were proposed as a pragmatic approach, i.e., focusing on specific target populations with high HCV prevalence and incidence (2). People living with HIV (PLWH) form one such target population with approximately 2.3 million PLWH being co-infected with HCV (6.2%). A particularly high incidence of HCV infections was observed in men who have sex with men (MSM) living with HIV (3,4).

In Switzerland, an HCV micro-elimination program, termed Swiss HCVree Trial, targeted to MSM living with HIV enrolled in the Swiss HIV Cohort Study (SHCS), was conducted (5–9): After the first screening phase ("Phase A") from October 2015 until June 2016, all participants with replicating HCV infection were offered treatment with direct-acting antivirals (DAA). This treatment phase ("Phase B") was accompanied by behavioral interventions towards risk reduction, consisting of four intervention sessions with trained counselors supported by an e-health tool. The results of the behavioral intervention and the discussion of its potential impact are published elsewhere (8,9). The trial finished with a re-screening from March until November 2017 ("Phase C") (**Figure 1**). The Swiss HCVree Trial led to a 57% and 84% decrease of incident and prevalent HCV infections, respectively (7).

The crucial question after the Swiss HCVree trial was, whether this short-term effort was enough for achieving a further decrease of HCV prevalence and incidence, or at least for maintaining the post-intervention level. To answer this question, we took advantage that the Swiss HCVree Trial was nested within the SHCS, a prospective, nation-wide cohort enrolling PLWH in Switzerland. After termination of the Swiss HCVree Trial in November 2017, the systematic HCV screening continued within routine SHCS follow-up visits, and DAA therapy was available for all participants with replicating HCV infection. In the present study, termed "Swiss HCVree post", we assessed whether the impact of the Swiss HCVree Trial on the prevalence and incidence of replicating HCV infections among MSM in the SHCS was sustained after termination of this trial.

Methods

Swiss HIV Cohort Study (SHCS)

The SHCS is a prospective, multi-center cohort study enrolling adult PLWH treated in Switzerland (10,11). In bi-annual follow-up visits, information about clinical, laboratory and life-style parameters are collected. Yearly plasma samples for research purpose are taken for every participant. All MSM are systematically tested for anti-HCV-IgG and/or HCV RNA at least once per year, all non-MSM participants are screened every second year. The SHCS was approved by the local ethical committees of the participating centers.

Study Population and Study Measurements within Swiss HCVree post

All MSM enrolled in the SHCS with a plasma sample available from 2019 were screened for replicating HCV infection, termed "Swiss HCVree Post" screen. MSM were defined as male participants with self-reported homosexual or bisexual preference at SHCS enrolment or most likely source of HIV transmission being a homosexual contact. To determine the point prevalence in 2019, all Swiss HCVree Post plasma samples were processed using the Cobas Roche HCV test with a limit of quantification of 15 International Units (IU)/mL. Samples were pooled in batches of 5 samples, leading to a nominal detection limit of 75 IU/mL. To determine the incidence rate over time, Swiss HCVree Post screening results were combined with routinely available HCV test results for MSM recorded in the SHCS (**Figure 1**).

Definition of incident and chronic infections

All participants with a replicating HCV RNA in the Swiss HCVree post screen, defined as an HCV RNA result of 75 (IU)/mL or higher, were further analyzed. All earlier HCV RNA and anti-HCV-IgG results recorded in the SHCS database were considered in addition to the medical history of the patients communicated by the treating physician. A *primary incident infection* was defined as having a replicating HCV RNA in Swiss HCVree post and either 1) both only non-replicating HCV RNA and negative anti-HCV-IgG test results before 2019 recorded in the SHCS, or 2) no previous HCV test available in the SHCS. An *incident re-infection* was defined as having a replicating HCV RNA in Swiss HCVree Post with a previous non-replicating HCV RNA and positive anti-HCV-IgG result recorded in the SHCS. A *prevalent infection* was defined as replicating HCV RNA in Swiss HCVree Post with previous replicating HCV RNA and positive anti-HCV-IgG results recorded in the SHCS. All medical records of patients with replicating HCV in Swiss HCVree Post were discussed with the treating physician to ensure correct classification of the infections.

Phylogenetic Analysis of HCV Infections

All incident HCV infections with genotype 1a were sequenced using Illumina technology. RAxML was used to infer the maximum likelihood phylogenetic trees assuming a general time reversible model with invariant sites and gamma-distributed substitution rates with four categories. The estimate of the best tree was then based on one hundred replicates including bootstrap values for each bipartition. An in-depth phylogenetic analysis was performed to estimate the number of domestic and international transmission links as defined in (12).

Statistical Analyses

Statistical analysis was performed using R (version 3.4.4). P-values to assess differences between participants with replicating HCV RNA and those with non-replicating HCV RNA were calculated using Fisher's exact test (categorical variables) and Wilcoxon rank test (continuous variables). Statistical significance was set at $p < 0.05$. The incidence rates, expressed in 100 person-years (py), for primary incident and incident re-infections were calculated using parametric survival models with exponentially distributed waiting time. The time at risk started with the first negative HCV test available in the SHCS (either negative anti-HCV-IgG, or negative HCV RNA), until the most recent information available (SHCS download August 2021). The time point of HCV infection was set to the midpoint between the last negative and first positive HCV test available. For the incidence rate of re-infection, the time at risk started 6 months after termination of HCV treatment, provided suppressed HCV viral load.

Results

Screening results of Swiss HCVree Post

Of the 4804 MSM active in the SHCS in 2019, 4641/4804 (96.6%) had available plasma samples in the biobank of the SHCS and were included in Swiss HCVree Post. Replicating HCV infection was identified among 28/4641 participants, leading to a point-prevalence of 0.60%. Of these, 11 (0.24%) infections were categorized as incident HCV infections (9 primary incident, 2 incident re-infections) and 17 (0.37%) as prevalent HCV infections (**Figure 2A**). The baseline characteristics of the Swiss HCVree Post participants are presented in **Table 1**.

Comparison of the HCVree screening phases

Results from the Swiss HCVree Trial are summarized in **Figure 2A** and presented in (7). Of note, 1463/4641(31.5%) participants were screened in Swiss HCVree Post, but had not been screened in the

Swiss HCVree Trial. The majority of these participants screened newly in Swiss HCVree Post were registered in the SHCS only after the Swiss HCVree Trial start (53.2%) or were missed in the Swiss HCVree Trial (36.2%, see (7) for reasons of missed screen). Vice versa, 537 participants were screened in the Swiss HCVree Trial, but not in Swiss HCVree Post. Reasons for this are drop-outs (71.8%), as well as missing plasma samples (18.1%), and few cases of misclassification of MSM status or delayed data entry. In total, 2812/4641 (60.6%) participants were screened in all three screening phases (**Figure 2B**). **Supplementary Table 1** summarizes characteristics of participants in the Swiss HCVree Trial, Swiss HCVree Post, or both trials. Of the 28 participants with replicating HCV RNA in Swiss HCVree Post, 7 had already a replicating HCV RNA in the Swiss HCVree Trial (**Figure 2C**). Looking at the intersection of the study participants (N = 2812) in all three phases, the prevalence of HCV infections was 144/2812 (5.1%) in Phase A, 27/2812 (1.0%) in Phase C, and 10/2812 (0.4%) in the Swiss HCVree Post.

Detailed information on participants with replicating HCV infection in Swiss HCVree Post

All participants with a replicating HCV RNA in Swiss HCVree Post had positive HCV antibodies at the time-point of the HCV RNA assessment. In **Figure 3**, the detailed HCV screening and treatment history of these 28 patients is visualized. Of the 9 participants with a primary incident infection, 5 registered newly in the SHCS in 2019 (ID 1- ID 5 in **Figure 3**), none of these infections were known to the treating physician before. We observed two HCV re-infections, one of which received HCV treatment for the earlier infection (ID 11), the other one experienced spontaneous clearance of the infection. Of the 17 participants with prevalent infections, 3 were registered in the SHCS after the start of the Swiss HCVree Trial (ID 12-14). Moreover, 7/17 had already been screened in the Swiss HCVree Trial: 4 with replicating HCV RNA and subsequent successful treatment (ID 15–18), 2 with replicating HCV RNA, but no treatment (ID 19-20), and one patient had a non-replicating HCV RNA in the Swiss HCVree Trial, but replicating in 2018 (ID 21). The remaining 7/17 patients did not participate in the Swiss HCVree Trial, 2 of them received HCV treatment earlier (ID 22-23), the others not (ID 24-28). The most frequent HCV genotype was 1a (14, 50%), followed by genotype 4 (8, 18.6%).

Risk factors associated with replicating HCV infection in Swiss HCVree Post

We observed no differences between participants with replicating HCV RNA and non-replicating HCV RNA regarding basic patient characteristics, including age and ethnicity (**Table 1**). Participants with replicating HCV RNA had less often a HIV RNA below 50 copies/mL (78.6% versus 95.7%, p = 0.001) and a lower CD4 cell count (517 versus 692, p = 0.002) at the time-point of HCV RNA assessment). Liver enzymes were significantly higher in participants with replicating HCV RNA (Alanine aminotransferase (ALT): 48.5 versus 25 IE/mL, p < 0.001; Aspartate aminotransferase (AST): 39 versus

25 IE/mL, p < 0.001). Participants with replicating HCV RNA reported more often previous intravenous drug use as compared to participants with non-replicating HCV RNA (21.4% versus 3.4%, p < 0.001). No differences were observed regarding non-intravenous drug use, inconsistent condom use and diagnosis of syphilis.

HCV incidence

We included 5352 participants with a total of 40483 py of follow-up time to assess the incidence of primary HCV incident infection and HCV incident re-infection from 2010 until 2020. The mean follow-up time was 7.6 years. In total, we observed 138 events for primary incident infections. There was a decline in primary incident infections from 0.54/100 py (95% CI = [0.33, 0.87]) in 2010 to 0.34/100 py (95% CI = [0.20, 0.59]) in 2015, to 0.31/100 py (95% CI = [0.17, 0.55]) in 2017 and 0.19/100 py (95% CI = [0.09, 0.39]) in 2019. See **Figure 4** for the incidence and number of primary incident and re-infections over time.

Phylogenetic analysis of incident HCV infections

A phylogenetic analysis of the 7 primary incident HCV infections with genotype 1a in Swiss HCVree Post was performed. Of these, 3 (42.9%) were in well-supported phylogenetic clusters, i.e. could be analyzed further with regards to characteristics of the transmission network. Two sequences classified as primary incident infections, were in a cluster consisting of 8 Swiss and 25 international sequences, indicating international transmission links. One sequence being classified as re-infection, was in a phylogenetic cluster of size 2, with the other sequence from another study participant, classified as prevalent infection, indicating a domestic transmission link.

Discussion

In Swiss HCVree Post, we screened all MSM enrolled in the SHCS for replicating HCV, using routinely collected plasma samples from 2019. We observed a point prevalence of 0.6% for replicating HCV in Swiss HCVree Post. From 2015 to 2017, the Swiss HCVree Trial was conducted towards the goal of achieving micro-elimination of HCV in MSM. In the Swiss HCVree Trial, all MSM enrolled in the SHCS were offered HCV RNA screening (Phase A), with an observed point prevalence of 4.8%. DAA treatment and behavioral intervention towards risk reduction was offered for all participants with replicating HCV RNA (Phase B), leading to a cure in 149 of 177 (84%) cases. In 2017, HCV RNA re-screening was offered (Phase C) with an observed point prevalence of replicating HCV RNA of 1.2%. Similar to the decrease of point prevalence, the HCV incidence of primary infections decreased from

0.34/100 py in 2015 to 0.19/100 py in 2019. This marked decrease in HCV prevalence and incidence two years after the Swiss HCVree Trial indicates a sustained effect on HCV elimination among MSM in the SHCS.

An increased access to DAAs can curb the HCV epidemic: In London, an overall reduction of 68% incident HCV cases among HIV-infected MSM was observed between 2015-2020, mainly as a result of wider access to DAAs (13). In the Netherlands, a sharp decrease of incident HCV infections among HIV-infected MSM in the ATHENA cohort was observed coinciding with wider access to DAAs (14). Similar trends of declining HCV incidence and prevalence following DAA roll-out were reported from Australia and France (15–17). However, the roll-out of DAAs seems not to be sufficient for achieving the WHO goal for 2030: In the case of London, the authors claim that targeted interventions are still necessary (13). Indeed, previous modeling work suggested that sustained reductions in high-risk behavior to prevent exposure to HCV transmission could have a major impact to curb the epidemic even without increasing access to treatment (18). The Swiss HCVree Trial combined a treatment as prevention strategy with high access to HCV treatment and accompanied these interventions with a comprehensive risk-reduction program. Hence, generalized screening programs combined with targeted intervention programs are needed to achieve early identification, access to treatment and reduction in high-risk behavior to prevent further infections on the long-run.

The point prevalence of 0.6% in 2019 observed in Swiss HCVree Post indicates a sustained effect of the Swiss HCVree Trial. Compared to the prevalence of 1.2% at the end of the Swiss HCVree trial in 2017, there was even a further decline in the point-prevalence and also in the incidence rate of new infections. Despite this promising trend, the results also highlight the persistence and complex challenge of the ongoing HCV epidemic: For 17/28 patients with replicating HCV RNA in Swiss HCVree Post, the infection was already detected before 2019, and 6/17 had already a replicating HCV RNA in the Swiss HCVree Trial, indicating that both re-infection and difficulties concerning HCV treatment success still occur, albeit rarely.

Looking at the screening and treatment history of participants with replicating HCV RNA in Swiss HCVree Post, it becomes clear that complicated medical histories, comorbidities, adherence problems and other risk factors play an important role for the cure and prevention of HCV infections: Participants with replicating HCV RNA had a lower CD4 cell count and more often replicating HIV RNA as compared to participants with non-replicating HCV RNA, suggesting HIV treatment difficulties, potentially also reflecting HCV medication adherence difficulties. Moreover, a fifth of the patients with replicating HCV RNA reported previous intravenous drug use in the routine SHCS questionnaire. Despite

the extensive harm reduction program in Switzerland, HCV infection through needle sharing might still be a problem and might be linked to the increase in the use of sex-enhancing intravenous drugs ("Chemsex") observed among MSM in the SHCS (19–21). MSM reporting the use of Chemsex drugs, even in the case of occasional use, should hence be preferentially screened for HCV. The phenomenon Chemsex might also indicate that HIV-uninfected MSM are now at higher risk of acquiring HCV, in contrast to estimations in Switzerland in 2014, when no significant higher prevalence was observed in HIV-uninfected MSM as compared to the general population (22). The need to address HIV-uninfected or HIV-undiagnosed MSM is also highlighted by our finding that 5 out of the 9 participants with primary incident infection were registered in the SHCS only in 2019.

A further obstacle for achieving HCV micro-elimination could be loss to follow-up. Around 10% of MSM participating in the Swiss HCVree Trial could not be screened in Swiss HCVree Post due to loss of follow-up. In the Netherlands, re-engaging MSM lost to follow-up was pointed out to be one priority towards achieving micro-elimination (23). Another hurdle to overcome are international transmission links: In Swiss HCVree Post, a phylogenetic analysis of genotype 1a HCV infected-participants revealed that two MSM with a primary incident infection were in a well-supported phylogenetic cluster with international transmission links. Though small numbers, this indicates that international transmission persists, emphasizing the necessity for concerted international efforts to reach the WHO HCV elimination goals.

A strength of our study is that using the longitudinal information and biobanked plasma samples from the SHCS, we could assess the long-term effect of a previously conducted nation-wide trial. The long-term incidence of HCV infections could be assessed, and risk factors for replicating HCV infection could be tested. One potential limitation is that in the Swiss HCVree Trial, the Abbott RealTime HCV test with a limit of quantification of 12 IU/mL was used, as compared to the Roche Cobas HCV test with the limit of quantification being 15 IU/mL in Swiss HCVree Post. Moreover, by pooling samples in 5 and hence raising the detection limit to 75 IU/mL we might have missed some low-level HCV viremia infections cases. Moreover, new registrations and drop-outs over time lead to changing characteristics of the study population (Supplementary Table 1), leading to potential over- or underestimations of incidence rates over time.

To summarize, the systematic screening and testing in the Swiss HCVree Trial followed by continuous surveillance and DAA treatment in the SHCS resulted in a sustained marked reduction in HCV incidence and prevalence. Despite some remaining challenges, Switzerland is on track to achieve HCV micro-elimination in MSM living with HIV.

NOTES

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Members of the Swiss HIV Cohort Study

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Ethical statement

The SHCS was approved by the local ethical committees of the participating centres: Ethikkommission beider **Basel** ("Die Ethikkommission beider Basel hat die Dokumente zur Studie zustimmend zur Kenntnis genommen und genehmigt."); Kantonale Ethikkommission **Bern** (21/88); Comité départemental d'éthique des spécialités médicales et de médecine communautaire et de premier recours, Hôpitaux Universitaires de **Genève** (01–142); Commission cantonale d'éthique de la recherche sur l'être humain, Canton de **Vaud** (131/01); Comitato etico cantonale, Repubblica e Cantone **Ticino** (CE 813); Ethikkommission des Kantons **St. Gallen** (EKSG 12/003); Kantonale Ethikkommission **Zürich** (KEK-ZH-NR: EK-793), and written informed consent was obtained from all participants.

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Conflicts of interest

JSF reports support for this work from Merck. MS reports support for attending meetings and/or travel from Gilead Sciences; and participation on an advisory board (payment to institution) for Gilead

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Figure 1

Figure 1*: Overview of the different screening phases in the Swiss HIV Cohort Study (SHCS): The Swiss HCVree Trial was a prospective HCV elimination trial among men who have sex with men (MSM) in the SHCS, comprising of a screening phase (Phase A), a treatment and intervention phase (Phase B) and re-screening phase (Phase C). In Swiss HCVree Post, HCV RNA screening was performed retrospectively from prospectively collected plasma samples for MSM in the SHCS. Routine HCV screening results are obtained once per year of each active SHCS participant.*

Figure 2: *A) Overview of the results from the Swiss HCVree Trial and Swiss HCVree Post: The Swiss HCVree Trial started with systematic screening from October 2015 to June 2016 (Phase A). After Phase B (treatment phase), a re-screening was done in March until November 2017. Swiss HCVree Post was performed in 2019. The top numbers indicate the total numbers of participants screened, the bars indicate the number of participants with replicating HCV RNA. B) Overlap between the participants in the three screening phases and C) Overlap of the participants with replicating HCV RNA in the screening phases. Swiss HCVree Trial - Phase A: October 2015 – June 2016, Swiss HCVree Trial - Phase C: March - November 2017, Swiss HCVree Post: Jan – Dec 2019*

Figure 3: *Detailed history of hepatitis C (HCV) screening and treatment in all participants with a replicating HCV RNA in the Swiss HCVree Post screen. The timeline for each participant starts at Swiss HIV Cohort Study (SHCS) registration. The red full circle indicates the Swiss HCVree Post sample, other red circles indicate earlier replicating HCV RNA results. Blue circles indicate non-replicating HCV RNA results. Red and blue crosses indicate positive and negative anti-HCV results, respectively. The green cross indicates the start of HCV treatment. The blue shaded area indicates the screening phases of the Swiss HCVree Trial, the red shaded area indicates Swiss HCVree Post.*

Figure 4: *Incidence rate of primary hepatitis C infections, re-infections and all infections combined among men who have sex with men (MSM) in the Swiss HIV Cohort Study (SHCS). The number of events is indicated at the top of each figure. The Swiss HCVree Trial took place from October 2015 until November 2017, the Swiss HCVree Post screen took place in 2019. CI = Confidence Interval*

1

2 **Table 1**

Characteristic		*Data available*	*All HCVree post patients*	*Non-replicating HCV RNA*	*Replicating HCV RNA*	*p value*
Total			4641	4613	28	
Birth year, median (IQR)		4641	1967 [1961,1977]	1967 [1961,1977]	1969 [1961,1975]	0.78
Registration year, median (IQR)		4641	2008 [2000,2014]	2008 [2000,2014]	2006.5 [1997.75,2018.25]	0.95
Ethnicity, n (%)	white	4636	4134 (89.1%)	4109 (89.1%)	25 (89.3%)	1
	black		86 (1.9%)	85 (1.8%)	1 (3.6%)	
	Asian		171 (3.7%)	170 (3.7%)	1 (3.6%)	
	Hispanic		240 (5.2%)	239 (5.2%)	1 (3.6%)	
HIV-related information						
HIV diagnosis year, median (IQR)		4641	2006 [1998,2012]	2006 [1998,2012]	2005.5 [1996.25,2015.5]	0.97
On ART, n (%)		4641	4615 (99.4%)	4587 (99.4%)	28 (100%)	1
HIV viral load <50 copies/ml, n (%) at time-point of HCV screening		4641	4436 (95.6%)	4414 (95.7%)	22 (78.6%)	**0.001**
CD4 at time-point of HCV screening, median (IQR)		4641	692 [528,886]	692 [529,887]	517 [391.5,711.5]	**0.002**
CD4 nadir, median (IQR)		4638	254 [147,377.75]	254 [148,377.75]	165 [106.75,367.25]	0.18

Liver-related data						
Liver enzymes, median (IQR)	ALT	4594	25 [19.05,35]	25 [19,34]	48.5 [34,75]	< **0.001**
	AST	4578	25 [21,30]	25 [21,30]	39 [27.5,64.5]	< **0.001**
ALT or AST > 50 U/L, n (%)		4578	425 (9.2%)	410 (8.9%)	15 (53.6%)	< **0.001**
History of Hepatitis B, n (%)		4160	1710 (36.8%)	1697 (36.8%)	13 (46.4%)	0.07
Other risk factors						
Ever reported intravenous drug use, n (%)		4641	165 (3.6%)	159 (3.4%)	6 (21.4%)	< **0.001**
Ever reported non-intravenous drug use, n (%)		4641	2049 (44.1%)	2035 (44.1%)	14 (50%)	0.57
Inconsistent condom use with occasional partners 2018-2019, n (%)		4641	1858 (40%)	1842 (39.9%)	16 (57.1%)	0.08
Syphilis, n (%)		4641	2110 (45.5%)	2098 (45.5%)	12 (42.9%)	0.85

Table 1: Basic, clinical and laboratory characteristics of the 4641 participants in Swiss HCVree Post, stratified by screening result;

HCV = Hepatitis C, IQR = interquartile range, n = number, ART = Anti-retroviral therapy, AST = aspartate-aminotransferase; ALT = alanine-aminotransferase

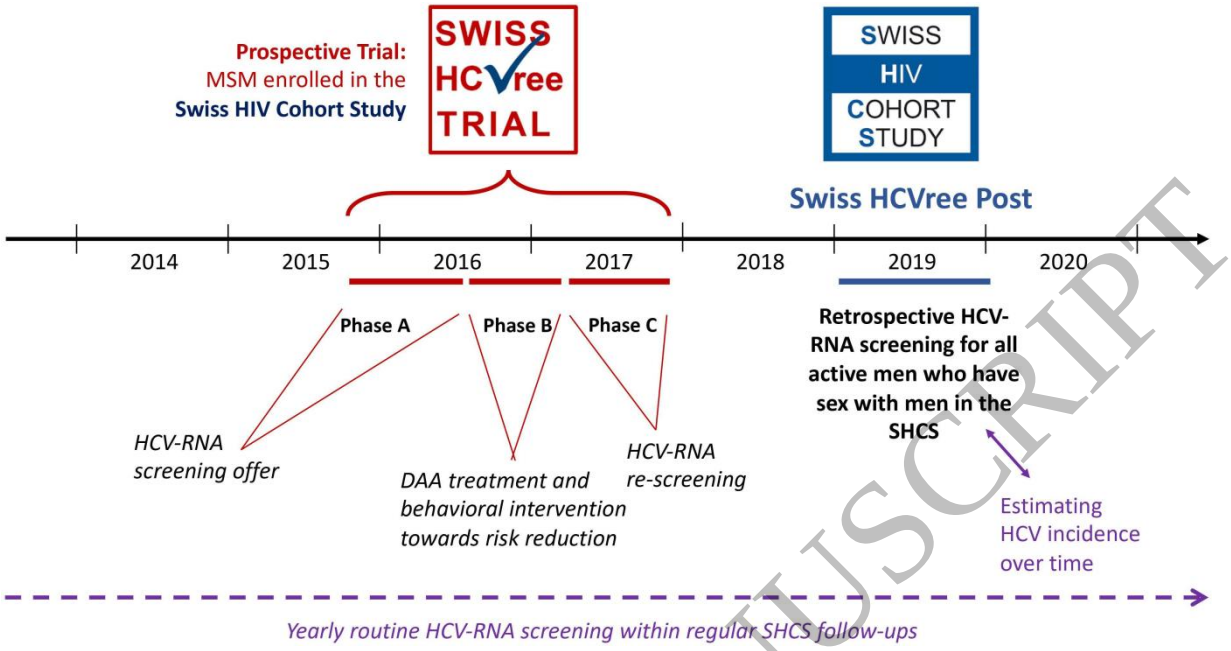

Figure 1
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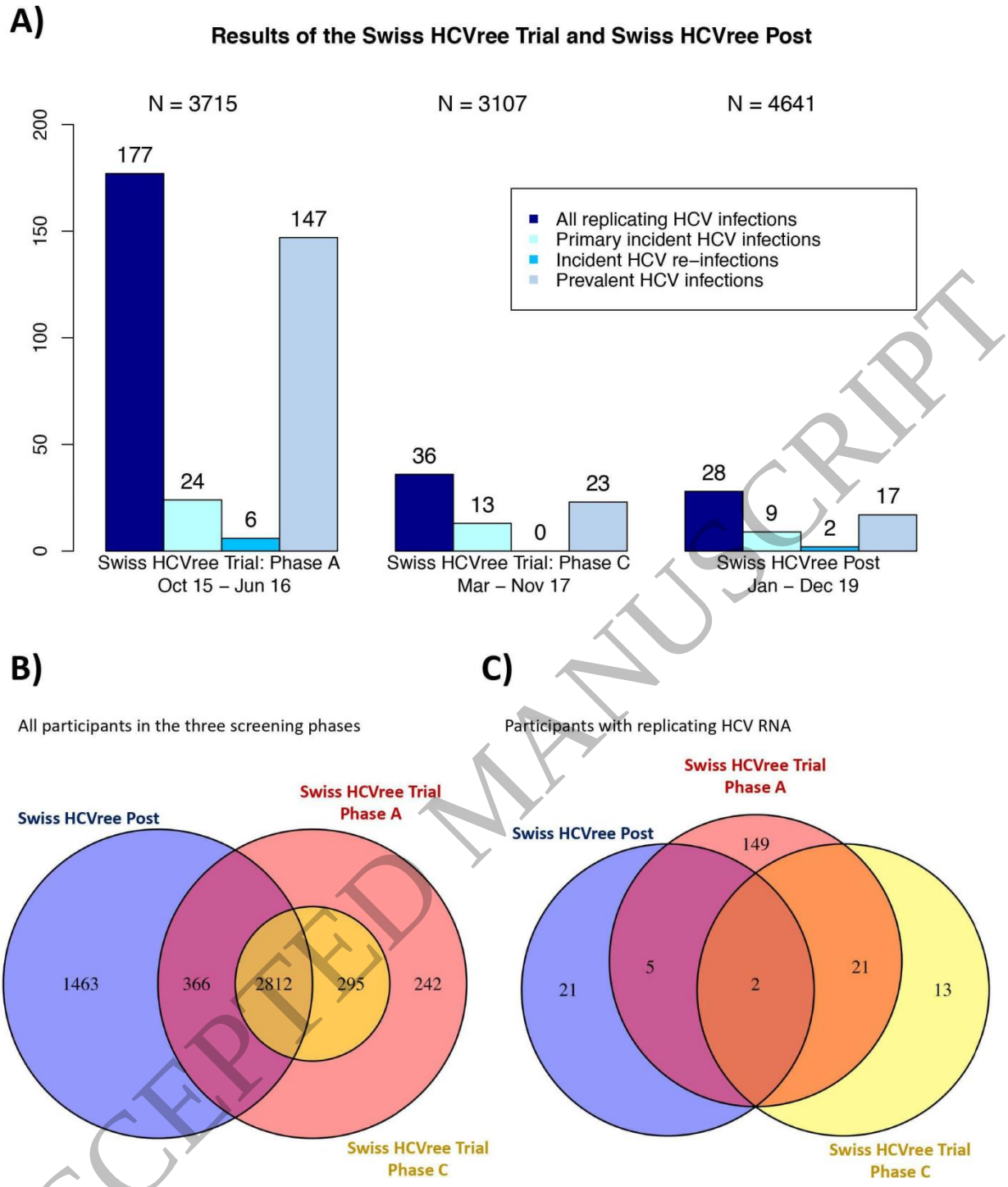

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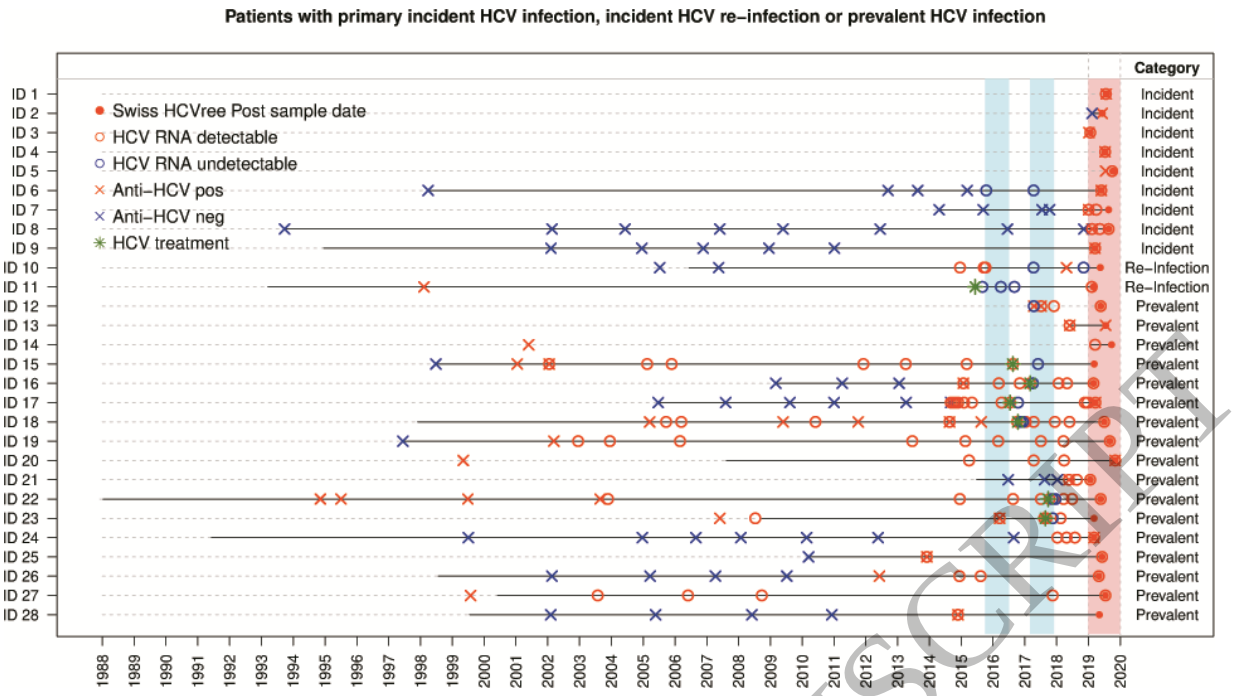

Figure 3
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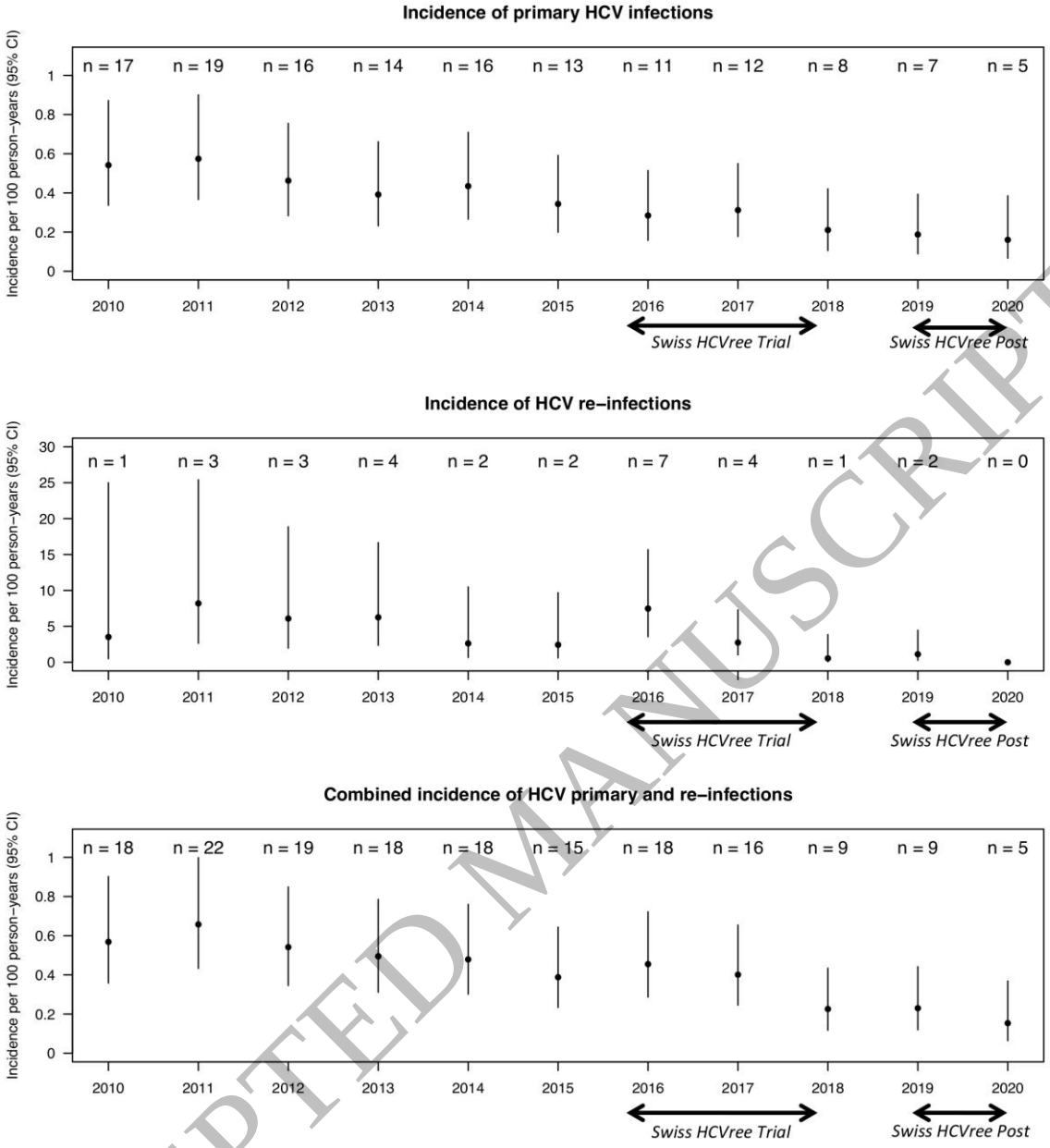

Figure 4
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