Late presentation for hepatitis C treatment: prevalence and risk factors in the Swiss Hepatitis C Cohort

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Abstract: OBJECTIVE Patients with 'late presentation' (LP) of chronic hepatitis C infection (HCV) have already developed advanced liver disease before receiving direct-acting antiviral (DAA) treatment. Even after successful treatment, the risk of morbidity and premature death remains elevated, leading to an unnecessary disease burden. This study aimed to assess the prevalence of LP within the prospective observational Swiss Hepatitis C Cohort (SCCS) and evaluate risk factors as determinants of LP. METHODS Treatment-naïve participants of SCCS who received DAA treatment between 2014 and 2019 were included. Demographic, clinical and behavioural data were compared between the LP and non-LP strata. LP prevalence was calculated over time and by year. LASSO regression was used to identify potential risk factors for LP, and odds ratios were calculated by refitting logistic regression models. RESULTS In this explorative, retrospective case-control study using data of n = 5829 SCCS members, a total of 21.3% received their first HCV treatment. The cumulative LP prevalence decreased from mid-2015 and stabilised at 46.5% (n = 579) by the end of 2019. Male gender, higher age and a history of alcohol overuse were associated with a higher risk of LP. CONCLUSION Despite the study's limitations, LP prevalence was higher than anticipated, considering Switzerland's availability period and universal access to DAAs. Therefore, any HCV LP should be viewed as a healthcare system failure, primarily in high-income economies. As LP is directly linked to the disease burden, it must be included as a mandatory parameter in surveillance response systems of HCV elimination programs.

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Objective Patients with 'late presentation' (LP) of chronic hepatitis C infection (HCV) have already developed advanced liver disease before receiving direct-acting antiviral (DAA) treatment. Even after successful treatment, the risk of morbidity and premature death remains elevated, leading to an unnecessary disease burden. This study aimed to assess the prevalence of LP within the prospective observational Swiss Hepatitis C Cohort (SCCS) and evaluate risk factors as determinants of LP.
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Results In this explorative, retrospective case–control study using data of n = 5829 SCCS members, a total of 21.3% received their first HCV treatment. The cumulative LP prevalence decreased from mid-2015 and stabilised at 46.5% (n = 579) by the end of 2019. Male gender, higher age and a history of alcohol overuse were associated with a higher risk of LP.
Conclusion Despite the study's limitations, LP prevalence was higher than anticipated, considering Switzerland's availability period and universal access to DAAs. Therefore, any HCV LP should be viewed as a healthcare system failure, primarily in high-income economies. As LP is directly linked to the disease burden, it must be included as a mandatory parameter in surveillance response systems of HCV elimination programs. Eur J Gastroenterol Hepatol XXX: XXXX–XXXX

Introduction

Since the introduction of direct-acting antiviral (DAA) treatment in 2014, people with chronic hepatitis C virus (HCV) infection can be treated with unprecedented success.

As DAAs are highly effective and well tolerated, almost no clinical barriers seem to be left to treat all affected persons. The overall effectiveness of DAA treatment is a cornerstone of the WHO's goal to eliminate viral hepatitis as a public health threat by 2030 [1], and the promising 2021 WHO progress report on viral hepatitis [2] shows that treatment uptake since 2015 has increased almost 10-fold. This treatment scale up has been analysed as sufficient to reverse the trend of increasing mortality of HCV for the first time. A recent modelling-based study which examined changes in HCV burden in different European countries has found that the number of successfully treated patients has surpassed the number of chronically infected patients by 2020 in the UK and by 2019 in Germany and Spain [3].

In the WHO European region [4], the estimated prevalence of HCV in 2021 ranged from 1.2 [5] to 1.3% [2], with approximately 11 million individuals still being chronically infected. According to epidemiological modelling, around 30% of the infected people are diagnosed and between 1.1 and 4.9% are treated yearly [6,7].

HCV infections should be treated promptly to limit the risk of developing liver damage and extrahepatic consequences [8]. Thus, current national and international guidelines recommend treating all individuals with a chronic HCV infection and a life expectancy beyond 1 year [9]. Chronic viral hepatitis, however, caused by HCV may remain clinically silent for decades, leaving most people unaware of their potentially life-threatening medical condition and their overall heightened risk of morbidity and premature death [10]. Because HCV affects not only the liver but also extrahepatic organs such as cardiovascular, renal, metabolic or neurological systems [11,12], those infected may suffer from unspecific symptoms, which are not easily recognised as being due to an underlying HCV infection. This contributes to the low diagnosis rate, which is a significant barrier in many countries to

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reducing the HCV disease burden [13]. Timely linkage to care is essential, as in patients who have already developed liver cirrhosis before treatment, the risk of hepatocellular carcinoma (HCC) remains elevated even after treatment and requires ongoing HCC surveillance [14].

The concept and definition of HCV 'late presentation (LP) for care' were introduced in 2017 by a consensus group endorsed by The European Association for the Study of the Liver [15] to collect and compare epidemiological data on untreated HCV patients who already suffer from liver-related sequelae of the infection and to monitor this population. The LP population has already developed advanced or late-stage liver disease before entering specialised care and receiving DAA treatment. Recent studies using the LP definition have found the prevalence of LP ranging from 25 to 47.8% in different European populations and settings [16–19].

So far, there is insufficient data in Switzerland on the prevalence of LP of HCV infection in the DAA era. Therefore, this study aimed to quantify the prevalence of LP within the prospective observational Swiss Hepatitis C Cohort (SCCS) [20] since the introduction of DAAs in 2014. The prevalence of LP was quantified in the treatment-naive population of SCCS before DAA treatment started. Demographic, clinical and behavioural factors as LP determinants were assessed and analysed to understand this high-risk patient group better.

Methods

Study population

The SCCS is a prospective cohort of about 5800 patients, established in 2000. The cohort is designed as a systematic longitudinal study enrolling patients with positive HCV serology from all academic outpatient clinics in Switzerland (Basel, Bern, Geneva, Lausanne and Zurich), two large regional hospitals, affiliated smaller hospitals and private physicians caring for HCV patients. Cohort entry and HCV treatment are independent (i.e. entry is not a prerequisite for treatment and vice versa), and some members are in the cohort for many years before starting treatment, while others start treatment with cohort entry.

We performed an explorative, retrospective case–control study of existing data (secondary analysis) from the SCCS data set. We included participants of SCCS chronically infected with HCV, aged ≥18 years and whose first DAA treatment had started between the 1 January 2014 and the 31 December 2019. Patients with any HCV treatment before entering SCCS or in whom previous HCV treatment was unclear because of missing information or incomplete data were excluded.

Ethical approval for collecting data and clinical samples with informed consent within SCCS was obtained at the cohort's inception from the competent ethics committees of all participating hospitals. The protocol of this study within SCCS has been approved separately by the Canton of Zurich Ethics Committee, and the study was conducted following the Declaration of Helsinki.

Definitions

The primary outcome of our study was the presence (vs. absence) of HCV 'LP for treatment', which we defined, adapting EASL's concept of 'LP for care' [15], as the presence of at least one of the following criteria in a treatment-naïve patient either at the time of SCCS entry (if treatment was initiated at that moment) or at the last consultation before HCV treatment initiation (if patient was already in cohort for a longer period before treatment): primary liver cancer, liver cirrhosis, (history of) fibroscan with a liver stiffness of ≥9.5 kPa, (history of) liver biopsy with a METAVIR fibrosis score of F3 or higher or (history of) gastrointestinal haemorrhage, jaundice, portosystemic encephalopathy or ascites as signs of decompensated cirrhosis. HCV LP was defined as absent (non-LP) in patients not meeting any of the above criteria.

At the start of their DAA treatment, we collected all included patients' demographic, clinical and behavioural data. Alcohol overuse was defined as a self-reported history of ever having consumed more than 20 g of alcohol per day for more than 1 year. Intravenous and intranasal drug use were defined as self-reported episodes of intravenous or intranasal drug consumption, respectively, and imprisonment, treatment for depression and other psychiatric therapies were recorded according to health records.

Statistical analysis

Demographic (age, gender, education and origin), clinical (e.g. psychiatric treatment and HIV status) and behavioural data (e.g. substance use and history of alcohol overuse) were summarised for the whole study population using means and standard deviations or counts with percentages, as appropriate, and compared between patients with and without HCV LP.

LP prevalences overall and within 1 year, that is, the proportions of patients with LP among all patients whose therapy had already started at time t and among all patients whose treatment had begun within 1 year before t, were plotted graphically over time t.

To identify potential risk factors for HCV LP, we first fitted a logistic LASSO regression model to standardised variables in a stacked multiply imputed data set ($m = 30$) and used five-fold cross-validation to determine optimal shrinkage. Variables were selected for further analysis if their coefficients were nonzero in the model with minimal cross-validation error in terms of binomial deviance or, in the case of categorical variables, at least one coefficient of their one hot encoded dummy variables was nonzero. In a second step, to further assess the significance of the selected variables based on P values and to obtain coefficient estimates not affected by shrinkage, we refitted and pooled logistic regression models on the selected support in the same multiply imputed data sets. Variables with P values <0.05 (for at least one level, in the case of categorical variables) were then considered associated with the risk of HCV LP, and their odds ratios (ORs) were calculated. A logistic regression model with the same variables was fitted on complete cases as a sensitivity analysis.

All calculations were done with R, version 4.3.0,Vienna, Austria using the tidyverse_2.0.0 and the additional packages tableone_0.13.2, mice_3.16.0 and miselect_0.9.0.

Results

Study population

Of the total SCCS population at the end of 2019 (n = 5829), 1244 patients (21.3%) matched the eligibility criteria. Table 1 describes the study sample, stratified by LP status and with fractions of missing values per variable.

Late presentation

Figure 1 shows the development of both the overall (i.e. cumulative) LP prevalence and the LP prevalence within 1 year from April 2014 to December 2019 (Additional Table 1 in Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A970* presents the same data in numerical form). The overall LP prevalence decreased from mid-2015 and stabilised at 46.5% (n = 579) by the end of the study period.

The optimal LASSO regression model yielded nonzero coefficients for (levels of) age, gender, education, origin, treatment for depression, intravenous and intranasal drug use, tattoos or body piercings, other risk factors for HCV acquisition, alcohol overuse, HIV status, imprisonment and the duration of the HCV infection. Table 2 presents the corresponding ORs, together with ORs

Table 1. Demographic, clinical and behavioural data of the study sample

		All	LP	Non-LP	smd	Missing (%)
n		1244	579	665		
Age at SCCS entry (years)	∅ (SD)	47.9 (11.5)	50.1 (11.1)	46.0 (11.6)	0.36	0.1
Female	*n* (%)	509 (40.9)	208 (35.9)	301 (45.3)	0.19	0.0
Education[a]						
Primary	*n* (%)	272 (22.1)	137 (23.9)	135 (20.5)	0.10	1.1
Secondary		710 (57.7)	331 (57.8)	379 (57.7)		
Tertiary		241 (19.6)	102 (17.8)	139 (21.2)		
Other		7 (0.6)	3 (0.5)	4 (0.6)		
Origin[b]						
Swiss	*n* (%)	816 (66.6)	382 (66.7)	434 (66.6)	0.16	1.5
Western (excl. Swiss)		258 (21.1)	134 (23.4)	124 (19.0)		
Eastern		64 (5.2)	26 (4.5)	38 (5.8)		
Other		87 (7.1)	31 (5.4)	56 (8.6)		
Treatment (incl. psychotherapy) for depression	*n* (%)	358 (29.0)	176 (30.6)	182 (27.7)	0.06	0.9
Psychiatric treatment (excl. for depression)	*n* (%)	241 (19.6)	118 (20.6)	123 (18.8)	0.05	1.1
Intravenous drug use	*n* (%)	640 (51.9)	301 (52.3)	339 (51.5)	0.02	0.9
Intranasal drug use	*n* (%)	503 (45.9)	220 (44.1)	283 (47.5)	0.07	12.0
High-risk sexual behaviour	*n* (%)	157 (13.7)	68 (13.3)	89 (14.1)	0.03	8.2
Tattoo or body piercing	*n* (%)	390 (35.9)	166 (33.7)	224 (37.8)	0.09	12.7
Other risk factors for HCV acquisition	*n* (%)	917 (75.3)	414 (73.1)	503 (77.1)	0.09	2.1
Alcohol overuse	*n* (%)	614 (49.9)	316 (55.1)	298 (45.3)	0.20	1.0
HBs Ag positive	*n* (%)	18 (2.0)	9 (2.0)	9 (1.9)	0.01	27.3
HIV positive	*n* (%)	63 (7.2)	31 (7.4)	32 (6.9)	0.02	29.2
Drug substitution program (e.g. methadone)	*n* (%)	358 (28.9)	164 (28.4)	194 (29.4)	0.02	0.5
Imprisonment	*n* (%)	268 (21.8)	121 (21.1)	147 (22.4)	0.03	1.1
Time from HCV diagnosis to SCCS entry (years)	∅ (SD)	7.01 (7.74)	6.94 (7.77)	7.08 (7.72)	0.02	2.7

excl, esclusive; HCV, hepatitis C virus; incl, inclusive; LP, late presentation; SCCS, Swiss Hepatitis C Cohort; smd, standardised mean difference.
[a]Roughly ISCED-2011 1/2-4/5-8/other [21].
[b](Slightly) modified UN regional groups [4].

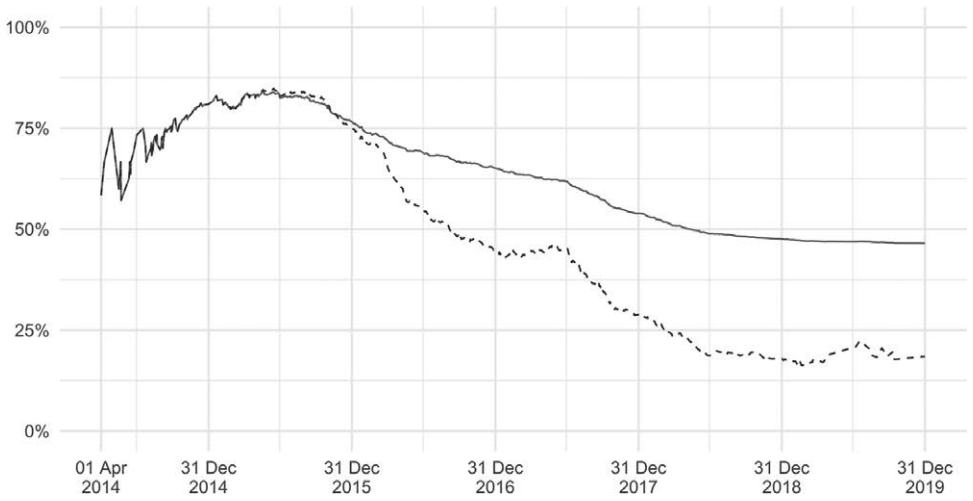

Fig. 1. LP prevalence in SCCS overall (solid line) and within 1 year (dashed line). A 'run-in' phase with two treatments starts before April 2014 is not shown.

Table 2. Variable selection using the LASSO and odds ratios (for late presentation vs. nonlate presentation) with *P* values (and significance codes) from logistic regression models

		Logistic regression			
	LASSO	Multiple imputation		Complete cases	
	OR	OR	*p*	OR	*p*
Age at SCCS entry (ORs per SD = 11.5 years)	1.48	1.55	<0.001***	1.72	<0.001***
Gender					
Male	1.51		Reference level		
Female	.	0.60	<0.001***	0.55	0.001**
Education[a]					
Primary	1.17		Reference level		
Secondary	.	0.81	0.167	0.81	0.291
Tertiary	0.87	0.66	0.032*	0.83	0.481
Other	.	0.94	0.944	0.59	0.718
Origin[b]					
Swiss	.		Reference level		
Western (excl. Swiss)	1.03	1.07	0.678	1.07	0.735
Eastern	.	1.00	0.990	1.14	0.730
Other	0.74	0.66	0.101	0.55	0.074
Treatment (incl. psychotherapy) for depression					
No	0.84		Reference level		
Yes	.	1.30	0.058	1.45	0.035*
Psychiatric treatment (excl. depression)					
No	.				
Yes	.				
Intravenous drug use					
No	0.94		Reference level		
Yes	.	1.23	0.213	1.32	0.200
Intranasal drug use					
No	1.11		reference level		
Yes	.	0.80	0.180	0.68	0.072
High-risk sexual behaviour					
No	.				
Yes	.				
Tattoo or body piercing					
No	1.02		Reference level		
Yes	.	0.91	0.536	0.96	0.817
Other risk factors for HCV acquisition					
No	1.07		Reference level		
Yes	.	0.92	0.542	0.86	0.438
Alcohol overuse					
No	0.73		Reference level		
Yes	.	1.46	0.003**	1.65	0.004**
HBs Ag status					
Negative	.				
Positive	.				
HIV status					
Negative	0.85		Reference level		
Positive	.	1.35	0.285	1.27	0.510
Drug substitution program (e.g. methadone)					
No	.				
Yes	.				
Imprisonment					
No	1.16		Reference level		
Yes	.	0.77	0.108	0.65	0.040*
Time from HCV diagnosis to SCCS entry (ORs per SD = 7.74 years)	0.93	0.89	0.067	0.92	0.355

HCV, hepatitis C virus; OR, odds ratio; SCCS, Swiss Hepatitis C Cohort.
*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.
[a]Roughly ISCED-2011 1/2-4/5-8/other [21].
[b](Slightly) modified UN regional groups [4].

and *P* values of the refitted logistic regression models (after multiple imputations and, as a sensitivity analysis, on complete cases). In the pooled refitted models, only higher age and alcohol overuse were associated with a higher risk and female sex and tertiary education with a lower risk of LP.

Except for the association with tertiary education, the sensitivity analysis essentially confirmed this finding and additionally suggested a higher risk for those treated for depression.

Discussion

In this explorative, retrospective case–control study using data of $n = 5829$ SCCS members, a total of 21.3% received their first HCV treatment from 2014 till the end of 2019. After the introduction of DAA, the overall (i.e. cumulative) LP prevalence in SCCS decreased from mid-2015 and stabilised at 46.5% ($n = 579$) by the end of 2019. Thus, regardless of the study's limitations, LP prevalence was higher than anticipated, considering the period of availability of DAAs. Among the assessed factors, male gender, higher age, a history of alcohol overuse and lack of post-primary education were associated with a higher risk of LP.

The strength of our study is the use of prospective, longitudinal data from a large national cohort population to evaluate trends and effects since the introduction of DAA. The study's starting point in 2014 must be considered when interpreting the results, as the prevalence of LP and the absolute number of treatment starts were presumably higher due to treatment delays in expectations of the highly effective DAAs. Furthermore, several HCV-related health policy changes in Switzerland during the period studied might have influenced the results: the reimbursement of DAAs in Switzerland was restricted to patients with a higher stage of fibrosis (≥F3 until September 2015, ≥F2 until October 2017), contributing to a delay in treatment uptake and presumably increasing the number of LPs as a result. Secondly, until the end of 2021, only designated medical specialists could prescribe DAA treatments, causing further delays in the cascade of care. Nowadays, access to DAA treatment is universal in Switzerland, and every physician can administer DAAs.

As the SCCS represents mainly tertiary treatment centres, a particular selection bias must be acknowledged: more complicated cases are often referred to specialised care, which could impact the prevalence of LP in the SCCS. Moreover, throughout the study period, the LP prevalence remained high even though every patient in our study had access to HCV treatment from the point of inclusion in the cohort. Our study does not provide an explanation for the slow decline in LP prevalence because, in this first evaluation of LP in SCCS, we did not investigate the critical period between diagnosis and cohort entry, for which the SCCS provides limited data, often self-reported from memory or incomplete (e.g. regarding the exact date of first diagnosis or disease stage at diagnosis).

Modelling studies provide data about estimated undiagnosed HCV infections, acting as a possible indicator for the prevalence of LP. In an Italian study from 2020, the estimated number of undiagnosed patients not linked to care was more than 280 000 [22]. Another study estimated that 42% ($n = 13'482$) of HCV-infected persons are undiagnosed in Switzerland [23]. Compared to similar studies from European countries using the EASL consensus definition of LP or an adapted version, our study's

overall prevalence was among the highest. Several other studies, however, found prevalences beyond what could be expected, considering the regions' access to diagnostics and care. In the German Hepatitis C Cohort [24], almost one-third of the study population presented themselves with severe liver disease at the starting point of the DAA treatment. The German Hepatitis C Registry showed similar results, with 28% [16] of the patients enrolled for treatment already suffering from long-term consequences of HCV. Likewise, other studies showed remarkable levels of LP, resulting from 11% [25], up to 32% [18], 37.4% [19] and 47.8% [26] prevalences.

Our study found a higher risk of LP clearly associated with increasing age, male gender, a history of alcohol overuse and lack of postprimary education. Overall, our findings echo the results of several studies for higher age and male gender and a history of alcohol overuse as risk factors for LP [18,24–27]. Further risk factors found in other studies are being diagnosed longer than 2 years before referral, genotype 3, MSM [25] and suffering from diabetes [26].

In our study, intravenous drug use was not identified as a risk factor for LP, implying that people who inject drugs (PWID) are well screened and treated. Although SCCS recruits primarily in tertiary centres, PWIDs are underrepresented in this cohort. In Europe, HCV prevalence is still high in the population of PWID, with up to 70% of chronic HCV infections [28], even though the incidence of HCV has declined in recent years due to widespread harm reduction measures for PWID and treatment programs [2,28]. In the Swiss cohort of people on opioid agonist therapy (SAMMSU) [29], LP was found in one of five newly diagnosed patients [30]. So, ongoing efforts in primary prevention, regular screening and comprehensive treatment schemes within this population sector are still crucial for the goal of eliminating viral hepatitis by 2030. In sum, identified risk factors have the potential to guide further measures to improve and streamline screening schemes and overcome hurdles on the patient's and provider's side within the cascade of care for HCV-infected patients.

After introducing the highly effective DAAs, pricing and policy issues had to be overcome, but the elimination of HCV seemed within reach, foremost in high- and middle-income regions. Since then, in the European region, many of those policy-driven barriers have been worked on, lowered or are no longer in place, as in Switzerland, where universal access to testing and treating is available. Nevertheless, our findings imply that unrestricted access, reimbursement of the costs and a well-tolerable treatment are not the overall conclusive factors for eliminating HCV [31] because still existing barriers to detecting affected persons and linking them to care leave a significant number of patients untreated and at risk of LP. Customised and comprehensive screening schemes are missing in many regions, including Switzerland. At the public health level, missing or inadequate guidelines and policies prevent screenings from being implemented and carried out as envisaged.

HCV elimination requires nationwide and regional hepatitis-specific action plans, including comprehensive approaches to disease awareness, prevention and adequate care [7] coupled with medical staff education and training. Parallel and complementary strategies should be in place to reach all affected persons in different subpopulations and at risk for LP, as every HCV-infected person with LP puts an avoidable burden on healthcare and society, associated with high costs arising from treating the chronic and severe sequelae of this well-treatable infection.

Furthermore, there are significant gaps in epidemiological data about LP in HCV worldwide. In future research, LP must become a mandatory coefficient for monitoring and evaluating the effectiveness of testing, screening and linkage to care, as well as for gauging the burden of disease. Within the population of LP, it is essential to identify vulnerable groups and determine still existing barriers to access to care. Accurate data on LP adds to adjusting deliberated regional and national strategies, monitoring the efforts of health authorities and policymakers and evaluating the overall quality of care for HCV-infected patients.

Conclusion

Overall, our results come into play for campaigning on public health, health service and patient levels to broaden the awareness, knowledge and motivation to diagnose and treat this potentially life-threatening disease timely. If those issues are not adequately addressed, Switzerland will not be on track to eliminate HCV [23].

For over 8 years now, hepatitis C has been a curable, chronic viral infection, and LP, with all its consequences, is now avoidable through early detection and prompt referral for treatment. Providing the appropriate cascade of care for patients infected with HCV should be possible in countries and regions with universal health access and the corresponding comprehensive policy. LP must be integrated as a mandatory parameter of well-functioning surveillance response systems of viral hepatitis elimination programs and as a parameter of quality of care in any national program to reach the goal of elimination. In our era, when HCV infection can be easily diagnosed and cured, any LP should be acknowledged as a healthcare system failure, at least in high-income countries.

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Conflicts of interest

N.B. has received research and travel grants from Gilead. The employer of P.B. has received project, research and travel grants from Gilead and Abbvie. For the remaining author, there are no conflicts of interest.

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