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The hepatitis C cascade of care in the Belgian HIV population: One step closer to elimination

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ABSTRACT

Objectives: The Belgian population of people living with HIV (PLHIV) has unrestricted access to direct-acting antiviral (DAA) treatment for hepatitis C virus (HCV) infection, since 2017. International literature claims that half of the patients remain untreated in high-income countries with unrestricted access to DAA. This study was initiated to provide an overview of the present situation in Belgium and recommendations for HCV care in PLHIV in other regions.
Methods: This was a retrospective, multicenter study of PLHIV in Belgium, from January 1, 2007 to December 31, 2018. The HCV cascade of care was examined.
Results: Out of 4607 unique PLHIV, 322 (7.0%) tested positive for HCV antibody and HCV RNA positivity was seen in 289 (6.3%). Of those with a proven HCV infection, 207/289 (71.6%) initiated treatment. Of the 171 (82.6%) persons with a sustained virologic response (SVR), 16 (9.4%) subjects were reinfected.
Conclusions: We present a care cascade of 4607 PLHIV in Belgium. Treatment initiation and SVR rates were high compared to other regions. Implementation of a national HCV register to track progress and yearly screening, especially in PLHIV with high-risk behavior, remains crucial. Identifying reasons for not initiating treatment is necessary to achieve elimination of HCV in PLHIV by 2030.

Introduction

Globally, 2–3 million new hepatitis C virus (HCV) infections are estimated to occur annually (WHO, 2017). Worldwide, the majority of patients have been iatrogenically infected, with the two most important risk groups for HCV infection being people who inject drugs (PWID) and people living with HIV (PLHIV) (Busschots et al., 2020). Globally, more than 6% of PLHIV is coinfected with HCV (Platt et al., 2016). According to a recent European review, HCV antibody (Ab) prevalence in PLHIV ranged from 2.9% to 43.4% (Mason et al., 2019). HCV Ab and RNA prevalence in the Belgian population is relatively low (1.0% and 0.3%, respectively), though there are no reasonable estimates of HCV prevalence in PLHIV (Muyldermans et al., 2019). In 2017, the number of PLHIV in Belgium was estimated to be 18,908. Of these, 89.0% were diagnosed and 11.0% were therefore, assumed to be unaware of their HIV serostatus (Sasse et al., 2018).

Until 2015, interferon (IFN)-based therapy was the standard of care to treat HCV infection in Belgium. However, not all coinfected

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patients could be treated with IFN or pegylated-IFN regimen (WHO, 2016). A large study in the United States found that just 43.9% of mono-infected patients were eligible for IFN treatment, in contrast to 28.4% of coinfected patients in between 1998–2003. Reasons for treatment ineligibility were anemia, decompensated liver disease, renal failure, active psychiatric disease, and recent drug abuse (Butt et al., 2011; Oramasionwu et al., 2014).

In Belgium, IFN-free, direct-acting antiviral (DAA) regimens have been available since early 2015. These regimes are well tolerated in mono-infected and coinfected patients (Pawlotsky et al., 2018). The exceptionally high viral clearance rate gives further ground for optimism. With these new, highly effective DAAs, HCV cure should be a realistic goal for most patients (Bertino et al., 2016; Pawlotsky et al., 2018). Between 2015 and 2017, there were restrictions on reimbursement of DAA regimens based on the fibrosis score (≥F2) for PLHIV (BCFI, 2015). Since January 2017, PLHIV have unrestricted and fully reimbursed access to DAA treatment in Belgium (RIZIV, 2018). Sacks-Davis et al. studied treatment uptake among HCV/HIV coinfected people in high-income countries (Australia, Canada, France, Georgia, Switzerland, and The Netherlands) with unrestricted access to DAAs. Results showed that treatment uptake in these countries were higher and SVR rates were promising compared with the data prior to DAA availability. However, approximately half (range 15%–79%) of the patients still remained untreated in the early DAA period (Sacks-Davis et al., 2018a).

This study was set up to overview Belgium's current situation as an HCV cascade of care for PLHIV in Belgium is unknown. By building a care cascade, the strengths and weaknesses of HCV care in the Belgian PLHIV can be exposed. From these perspectives, recommendations can be made for HCV care in other regions.

Methodology

Study design

This is a multicenter, retrospective study of PLHIV in three hospitals, two of which have an HIV reference center and one independent HIV reference center in Belgium, from January 1, 2007 to December 31, 2018. Patients aged 18 years or older, who visited the centers for a consultation with their infectious disease specialist during the study period were included. There were no specific exclusion criteria.

Data collection

Data were collected retrospectively from medical records of all patients over the age of 18 years and diagnosed with HIV at the Institute of Tropical Medicine (ITM) Antwerp, Jessa Ziekenhuis (JESSA) Hasselt, Universitair Ziekenhuis Leuven (UZL), and Ziekenhuis Oost-Limburg (ZOL) Genk.

Cascade of care was determined and covered the IFN period (2007–2014) and the DAA period (2015–2018). We chose 2007 as the starting point because of the implementation of European HCV screening guidelines for PLHIV in that year and owing to the lack of reliable and available patient records prior to 2007 (EACS, 2007). The year 2015 was chosen as the start of the DAA period since DAA treatment has been reimbursed since January 2015 in Belgium (BCFI, 2015). In the HCV cascade of care, we distinguished the number of HCV Ab positives, patients diagnosed with HCV infection, patients who initiated treatment, patients having achieved sustained virologic response (SVR), and the number of patients reinfected after achieving SVR.

We also included data on demographic, laboratory, and clinical data routinely collected by treating physicians: birth gender, year of birth, country of birth, year of diagnosis of HIV and HCV, probable year and country of transmission of HIV and HCV, transmission route of HIV and HCV (intravenous drug use, sexual practices, professional risk, accidental, transfusion, mother to child, tattoo/piercing, other or unknown), HCV genotype, FibroScan® results (cutoffs for HCV/HIV: F0–F1 = <7 kPa, F2 = 7–11.5 kPa, F3 = 11.5–14 kPa, F4 = >14 kPa) (Echosens, 2018), laboratory results concerning HCV (Ab and RNA), HCV treatment history and outcomes, the reason for not initiating DAA treatment, and presence of sexually transmitted infections (STI; hepatitis A and B, chlamydia, syphilis, genital herpes and warts, Trichomonas vaginalis, gonorrhea, human papillomavirus, and lymphogranuloma venereum — not tested or unknown). All data were filled out in an online clinical registry file, Castor EDC (2020), by one of the local investigators. We used the date of birth to identify potential duplicates. In accordance with guidelines for privacy legislation, this information was removed after checking for duplicates. Records were linked based on the date of birth and additional information such as gender and year of HIV infection. If the date of birth was the same but the additional information was not, both individuals were considered unique.

The protocol was submitted to the ethics committee of each participating center. Approval was obtained from all study locations (ITM (1265/18), JESSA (19.99-INFECT19.04), UZL (S61948) and ZOL (18/0068L)), and Hasselt University (CME2018-061). Informed consent was based on a presumed consent procedure as per Belgian regulation for retrospective studies.

Definitions

HCV diagnosis

The patient must have at least one positive HCV antibody test and/or HCV RNA test (the latter for active cases). The infection is defined as chronic if the virus is still detectable after six months.

Spontaneous clearance

The patient must have at least one positive HCV antibody result and an undetectable HCV RNA at the most recent laboratory test in the absence of treatment.

Sustained virologic response

An undetectable HCV RNA at 12 weeks (after 2015) or 24 weeks (before 2015) after treatment completion was confirmed with a sensitive HCV RNA lower limit of detection <15 IU/mL (conform EASL guidelines (Pawlotsky et al., 2018; Yoshida et al., 2015)).

HCV reinfection

Reinfection is the detection of a single detectable HCV RNA measurement 12 weeks after an SVR (SVR24 before 2015 and SVR12 after 2015) (Young et al., 2017).

Endpoints of the study

The primary objective of this study was to construct an HCV cascade of care for PLHIV in Belgium. By building a care cascade, the strengths and weaknesses of HCV care in Belgian PLHIV can be exposed. From these points, recommendations can be made for HCV care in other regions.

Statistical analysis

A cascade of care was built to identify the strengths and weaknesses of HCV care in HIV infected patients using descriptive analyses. To assess which factors influence DAA treatment uptake, a generalized linear mixed model with random intercept accounting for the different sites was used.

For JESSA, UZL, and ZOL, HCV incidence rates for each year of the study period were calculated. Yearly incidence rates for HCV seroprevalence were expressed as the number of new HCV Ab detections per 100 person-years (PY). The total number of diagnosed cases that year was divided by the total number of patients attending their HIV consultation that year and multiplied by 100. ITM provided the previously published incidence rates of their HIV infected men having sex with men (MSM) population between 2008 and 2017 (Apers et al., 2013).

To measure the impact of reimbursement criteria in the Belgian HCV/HIV coinfected population, the incidence rate ratio (IRR) and its 95% confidence interval (CI) were calculated, and to compare DAA treatment, uptake before and after full reimbursement was initiated. Therefore, treatment uptake was defined as the incidence of treatment initiations before and after the reimbursement criteria change. The IRR was calculated using the subgroup of patients who were diagnosed with HCV before 2017. An IRR greater than 1 indicates an increase in treatment uptake after full reimbursement of DAA treatment. An IRR was also used to compare reinfection incidence between DAA and IFN-treated patients.

Results

Patient characteristics of HCV/HIV coinfected patients

A total of 4,607 unique PLHIV visited one of the participating centers between 2007 and 2018. There were 322 (7.0%) patients with HCV/HIV coinfection. In this group, the average year of birth was 1971 ± 9.8, 100/322 (31.1%) patients were not born in Belgium, and 297/322 (92.2%) patients were males. FibroScan® scores were available for 148/322 (46.0%) patients, and HCV genotype was identified in 248/289 (85.8%) of the patients with HCV infection (Table 1).

In most cases (270/322; 83.9%), HCV's main transmission route was unknown or not stated in the medical records. For those with a known transmission route (52/322; 16.2%), unsafe sexual contact was the main route, followed by injection of drug, blood transfusion, and mother-to-child transmission in respectively 30 (57.7%), 16 (30.8%), 5 (9.6%) and 1 (1.9%).

Of the 297 HCV Ab-positive men, 253 (85.2%) were found to have had sexual contact with another man and were therefore defined as MSM. More than half of these MSM (149/253, 58.9%) were diagnosed with syphilis during the study period. The odds for sexually transmitted infections were higher in MSM than in men with heterosexual contacts causing syphilis (OR 16.78 CI 95% 7.38–53.77, $p < .001$), lymphogranuloma venereum (OR 10.78 CI 95% 2.82–284.39, $p = .005$), chlamydia (OR 8.26 CI 95% 2.73–63.16, $p = .002$), and gonorrhea (OR 7.21 CI 95% 2.37–55.11, $p = .003$),but the odds did not differ for hepatitis A or B, genital herpes or warts, human papillomavirus or trichomonas vaginalis. Eight out of the whole group of 322 (2.5%) HCV Ab positives died during the study period (reason unknown).

Table 1
Baseline characteristics of hepatitis C infection (n = 322).

Characteristics		n (%)
Gender	Male	297 (92.2)
	Female	25 (7.8)
Year of birth (mean ± SD)		1971 ± 9.8
METAVIR score (n = 148)	F0–F1	78 (52.7)
	F2	41 (27.7)
	F3	20 (13.5)
	F4	9 (6.1)
Genotype (n = 248)	1	5 (2.0)
	1a	144 (58.1)
	1b	14 (5.6)
	2	2 (0.8)
	2b	1 (0.4)
	3	4 (1.6)
	3a	5 (2.0)
	4	15 (6.0)
	4a/c/d	58 (23.4)

HCV incidence

For the PLHIV at JESSA, UZL and ZOL, the lowest and highest yearly HCV incidence rates were 0.57 (2007) and 2.28 (2017) new cases per 100 PY, respectively. A prominent peak in incidence for the MSM population at ITM was observed in 2009, with 2.93 new cases per 100 PY. However, a slight increase over the years showed a second peak in 2015, with 2.28 new cases per 100 PY (Figure 1).

HCV cascade of care

During the study period, 322 of the 4,607 (7.0%) patients tested positive for HCV Ab. Of the 322 HCV Ab positives, 289 (89.8%) had a positive HCV viral load at least once during the study period (Figure 2). Of 289 patients diagnosed with HCV viral infection, 207 (71.6%) received treatment (IFN-based before 2015 or DAA after 2015; Figure 3). Thirty-one (15.0%) received both IFN and DAA treatment. Reasons for not starting treatment were known for only eight patients. Four (1.4%) patients started therapy in 2019, and four (1.4%) died before treatment could be initiated.

Reinfection was detected in 16 patients with proven SVR, 13/47 (27.7%) after IFN-based treatment, and 3/133 (2.3%) after DAA treatment (Figure 3). Of all the 16 reinfections that occurred, 11 (68.8%) were caused by a different genotype.

Treatment uptake

During the study period, 207/289 (71.6%) patients received treatment. Three patients were successfully treated with IFN-based therapy before 2007. The incidence of DAA treatment uptake was 15.22 per 100 PY before 2017 versus 28.51 per 100 PY after 2017. This gives an IRR of 1.87 (95%CI 1.25–2.81, $p = .002$), indicating a significant increase of 87% in DAA treatment uptake following the change in reimbursement criteria. The odds for receiving HCV DAA treatment decreased with age (AOR 0.95 95%CI 0.91–0.98; $p = .005$), but was higher for patients with suppressed HIV viral load (AOR 13.59 95%CI 4.00–64.53, $p \leq .001$) and if other STIs were present (AOR 3.54 95%CI 149–8.83, $p = .005$).

Reinfection incidence

Reinfection incidence was 9.63 per 100 PY for those treated with IFN-based therapy and 1.40 per 100 PY for those treated with DAA. This gives an IRR of 0.15 (95%CI 0.04–0.51, $p = .001$), indicating a significant decrease of 85% in reinfections when treated with DAA instead of IFN.

Discussion

This multicenter, retrospective study included 4,607 PLHIV in a high-income country. The study population accounts for 27% of the total number of diagnosed HIV patients in Belgium. A substantial number (7.0%) of this study population was found positive for HCV Ab and 6.3% for HCV RNA. The majority (71.6%) was treated, and we found a high SVR percentage (82.6%). Reinfection after treatment with DAAs was relatively low, with 1.40 new cases per 100PY. Until 2015, there were many barriers to HCV IFN-based therapy and treatment uptake varied widely (Oramasionwu et al., 2014). Overall, treatment was initiated in 71.6% of the infected individuals

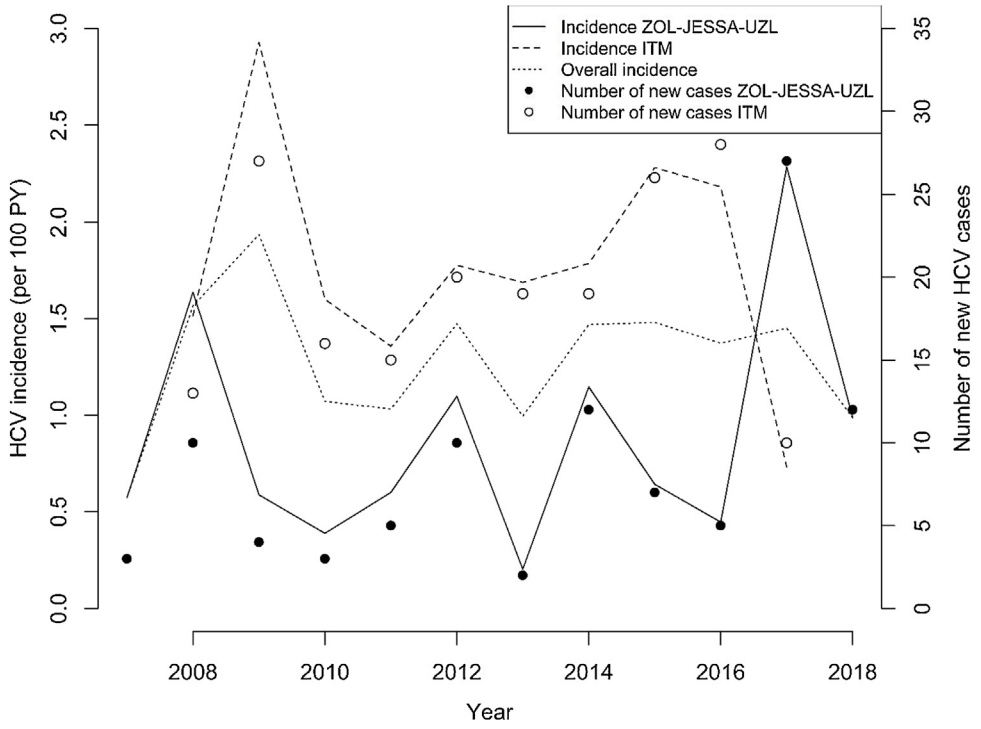

Figure 1. The yearly overall incidence rate and the yearly incidence rate of hepatitis c virus infection in the total HIV population in JESSA, UZL, and ZOL, and the HIV MSM population in ITM.
Abbreviations; ITM: Institute of Tropical Medicine; JESSA: Jessa Ziekenhuis; UZL: Universitair Ziekenhuis Leuven; ZOL: Ziekenhuis Oost-Limburg.

by the end of 2018, after two years of unrestricted DAA access. Our results are promising, given that in projects in Australia (40.0%), Canada (72.0%), Georgia (64.0%), and Switzerland (79.0%), a majority of the patients remained untreated, despite the broad availability of DAA treatment (Sacks-Davis et al., 2018a). Our number is more similar to the treatment uptake of the HEPAVIH cohort (85.0%) in France and to the treatment uptake of the treat 87%, found in a large group of 23,574 PLHIV in the Netherlands between 1998 and 2017 (Boerekamps et al., 2018). In addition, we showed an increase of 87.0% in DAA treatment following the change in compensation criteria, respectively, 15.22 per 100 PY for 2017 versus 28.51 per 100 PY after 2017. This emphasizes the importance of providing unrestricted access to DAA therapy in this population with an increased risk of HCV infection. We are confident that the treatment uptake will continue to increase, especially when there are no longer restrictions on reimbursement, as our results show. However, another point of attention may be that although the restrictions on reimbursement are eliminated in Belgium, DAA regimens can only be prescribed and initiated by a hepatologist and are only available in a hospital pharmacy. Access to treatment would improve, and patients would be able to obtain their medication more easily if treatment could be prescribed by other healthcare professionals and be available in local pharmacies. Our results may be underestimated as we had no data on treatment uptake for 25.6% of the study population.

The lack of data is mainly because the patients fail to follow-up. Patients move not only nationally, but also internationally, thus potentially changing physicians/centers. Failed follow-ups could be reduced by implementing a national register analogous to the ATHENA cohort in the Netherlands (Boerekamps et al., 2018).

SVR, after IFN-based treatment had been relatively low and was usually achieved in less than half of the treated patients ranging from 7.0% to 40.0% (Cachay et al., 2014; Mehta et al., 2006; Torriani et al., 2004). The SVR rate following IFN-based treatment in our study was, therefore, relatively high (57.3%). DAA therapy is associated with very high viral clearances of >90% (Bertino et al., 2016). The SVR rate following DAA treatment in this study seems slightly lower (85.3%). Although, when restricting analyses to patients with a known SVR result, 99.2% (132/133) achieved SVR. These results are in line with other studies where SVR rates were found ranging from 86% to 98% in other high-income countries (Sacks-Davis et al., 2018a).

Considering the shorter duration of treatment and the much greater tolerance of DAA therapy, a concern has emerged that enhanced therapy can increase risk-bearing behavior and a higher incidence of reinfection (Martin et al., 2018b). During the total study period, reinfection was present in 9.4%. This was slightly higher than that in studies from Canada and Spain, respectively 7% and 5% (Pineda et al., 2015; Young et al., 2017). However, reinfection incidence was 9.63 per 100 PY for those treated with IFN-based therapy and decreased to 1.40 per 100 PY for those treated with DAA. Over the years, prevention strategies such as regular HCV testing, harm reduction, and behavioral interventions were implemented to prevent new infections and reinfection after treatment (Martin et al., 2018a). This may also have potentially contributed to a decrease in the prevention of reinfection in this population. HCV elimination should be possible by upscaling HCV treatment combined with behavioral risk reduction for both PLHIV and the general population (Martin et al., 2018a; Sacks-Davis et al., 2018b).

The yearly incidence rates for the total PLHIV population in JESSA, UZL, and ZOL were lower than the yearly incidence rates for the MSM population in ITM. The incidence in ITM is probably higher because of a larger subpopulation with high risk factors (e.g., MSM, PWID) compared to the other centers' populations. In the coinfected population in ITM, 91.2% identified themselves as MSM compared to 46.2% in ZOL, 47.4% in JESSA, and 61.3% in UZL. In addition, the peak seen in 2017 for the total PLHIV population may

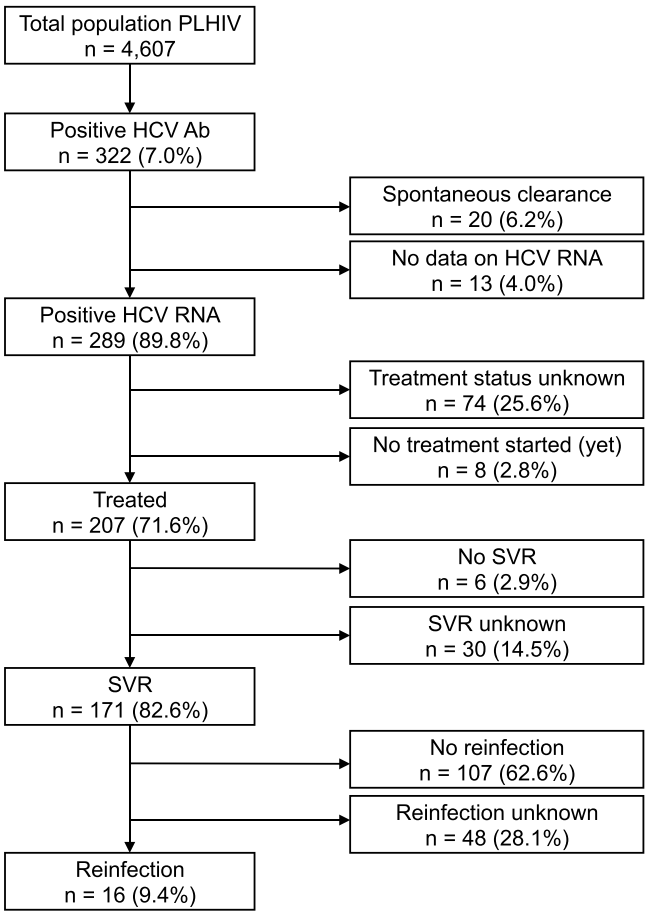

Figure 2. The flowchart accompanying the hepatitis C cascade of care in people living with HIV in Belgium.

be attributed to the fact that in that year, DAA treatment was reimbursed for the entire HCV/HIV coinfected population, leading to an increase in screening (RIZIV, 2018).

The HCV seroprevalence found in this study is similar to the prevalence found in neighboring countries, France (7.0%), the Netherlands (5.0%) and the United Kingdom (5.1%) (Mason et al., 2019; Platt et al., 2016). Besides, the prevalence of HCV Ab (7.0%) and RNA (6.3%) in PLHIV found in our study is many times higher than previously estimated in the general population in Belgium (1% and 0.3%, respectively) (Litzroth et al., 2019; Muyldermans et al., 2019).

We compared the genotypes found in our study to the genotypes of the Belgian PWID population (Robaeys et al., 2016). In our PLHIV population, the majority were infected with genotype 1a, followed by genotype 4 (a/c/d). This is similar to what was reported in international literature (Zhang et al., 2015). On the other hand, the majority of the PWID in the Belgian population was also infected with genotype 1a but followed by genotype 3 (Robaeys et al., 2016). Considering that genotype 1a is most common in both populations, we could speculate about an overlap of the two populations in Belgium. However, no transmission cluster analysis has yet been performed for HCV in PLHIV and more specifically for MSM in Belgium. Therefore, it is not clear whether this virus has been spilling over from local PWIDs or has been imported from foreign MSM contacts. Australian, Canadian, and the Dutch studies suggest that MSM acquire their HCV infection locally from both risk groups and common social networks (Jacka et al., 2014; Matthews et al., 2011; Vanhommerig et al., 2017). However, both risk groups seem to belong to different transmission networks in Germany and Romania (Paraschiv et al., 2017; Vogel et al., 2010).

A recent modeling study has shown that on an average, at least 8% of all the patients in need of treatment have to be treated per year in Belgium (Busschots et al., 2020), to reach the goals of the World Health Organization (WHO) to eliminate HCV by 2030 (reducing new infections by 90% and mortality by 65%) (WHO, 2016). A large part of our population has received treatment. However, we must remain aware of the gaps in the care cascade such as treatment uptake and possible reinfection after treatment. Future research, preferably prospective longitudinal studies, could investigate the uptake of treatment and the exact prevalence and incidence of reinfection after successful treatment. Besides, a national registry could map the progression to elimination as all initiatives are currently at local level. To date, such a register is not available in Belgium.

This study has several limitations. First, the study period started in 2007 due to a lack of reliable and available patient records prior to 2007. Secondly, we only collected more detailed data on the coinfected population. Each center knows its cohort of patients with HCV coinfection. Therefore, we have no detailed data on HCV screening among the general PLHIV population since we aimed to construct an HCV care cascade. Further, due to the study's retrospective nature, we were unable to collect data on persistent

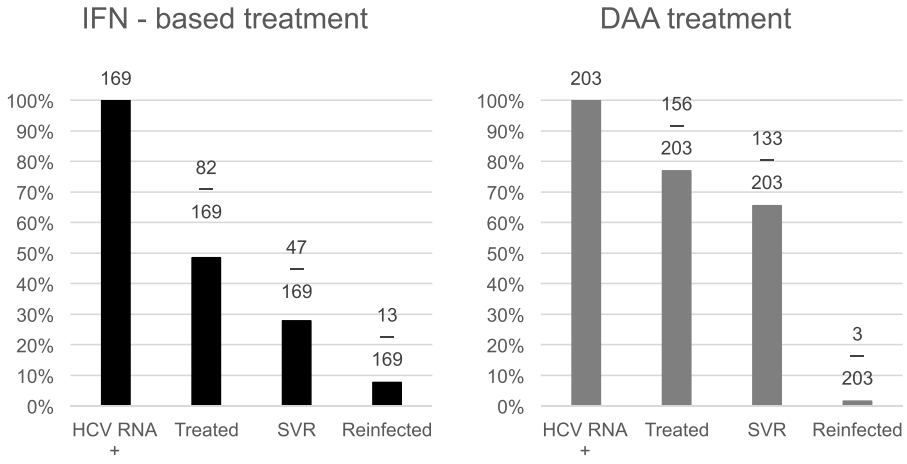

Figure 3. (a and b) The hepatitis C virus cascade of care for patients treated with interferon-based treatment (a) or direct-acting antivirals (b). In both graphs, 100% represents the number of HCV/HIV coinfected patients who require treatment.
Abbreviations — HCV RNA: hepatitis C ribonucleic acid; SVR: sustained virologic response; IFN: interferon; DAA: direct-acting antivirals.

risk behavior in MSM (e.g., unprotected anal intercourse with several partners, chemsex including slamming and fisting) and PWID (e.g., frequency of IDU, sharing paraphernalia). Therefore, we could not precisely describe the risk factors for HCV acquisition among our population.

However, risk factors for HCV acquisition among the MSM population at ITM (other STIs, anal douching, and intercourse with HIV-positive men) have previously been analyzed using a case-control study in 2015 (Apers et al., 2015). We also lacked data on (re)treatment in more than 25.6% of patients with detectable HCV RNA. This means that our number of patients treated may be an underestimation. However, there will still be a group of patients who have not been treated for various reasons. Identifying these reasons is necessary to eliminate HCV in PLHIV, especially in the MSM group with persistent risk behavior. Lastly, the reinfection incidence should be interpreted with caution. Due to the study's retrospective nature, we were unable to collect the exact date of reinfection. Therefore, the exact time until reinfection could not be taken into account, potentially leading to an overestimation of the decrease in reinfection incidence in the DAA era. Moreover, the overall prevalence of reinfection may be underestimated because we probably do not have an RNA determination of all the patients after SVR. Monitoring reinfection in this population, especially in those with persisting high-risk behavior is crucial to meet the HCV elimination goals of the WHO by 2030.

Nevertheless, we are not there yet, and extra effort needs to be made. Implementation of a national HCV register to track progress and yearly screening, especially in PLHIV with high-risk behavior, remains crucial. Besides, there are still a proportion of patients who have not been treated, and identifying the reasons are crucial. Moreover, HCV elimination by 2030 should be possible by upscaling HCV treatment combined with harm reduction for (HIV-positive) PWID and behavioral risk reduction for both PLHIV and the general population.

Funding

This study is part of the project G0B2317N funded by the Fund of Scientific Research — Flanders(FWO).

Ethical approval

The protocol was submitted to the ethics committee of each participating center. Approval was obtained from all study locations (ITM (1265/18), JESSA (19.99-INFECT19.04), UZL (S61948) and ZOL (18/0068L)), and Hasselt University (CME2018-061). Informed consent was based on a presumed consent procedure as per Belgian regulation for retrospective studies.

Conflict of interests

D.B. has received travel grants from AbbVie and Gilead Sciences, and research grants from Gilead Sciences; R.B. has received travel grants from AbbVie, Gilead Sciences, and Merck Sharp & Dohme (MSD), and research grants from Gilead and MSD; O.K. has received a travel grant from Gilead Sciences, and research grants from Gilead Sciences and CyTuVax BV; P.M. has received travel grants from Gilead, Viiv, MSD, and Janssen-Cilag, and consultancy agreements from Gilead, Viiv, and Janssen-Cilag; K.V.L. has received grants from MSD; E.V.W. has received travel grants from Gilead and MSD; F.N. has received research grants, consultancy agreements, and travel grants from UCB, Ipsen, Roche, Astellas, Ferring, Novartis, Janssen-Cilag, Abbvie, Gilead, CAF, Intercept, Gore, Bristol-Myers Squibb, (BMS), MSD Promethera Biosciences, Ono Pharma, and Durect; N.H. reports grants from GlaxoSmithKline (GSK), Johnson & Johnson pharmaceuticals, and Pfizer; G.R. has received research grants from AbbVie, Janssen Pharmaceuticals, MSD, and consultancy agreements from AbbVie, BMS, Gilead Sciences, and MSD. All other co-authors report no competing interests.

Statement of ethics

Approval was obtained from all study locations (ITM (1265/18), JESSA (19.99-INFECT19.04), UZL (S61948) and ZOL (18/0068L)), and Hasselt University (CME2018-061). Informed consent was based on a presumed consent procedure as per Belgian regulation for retrospective studies.

Author's contributions

D.B. and G.R. designed the study. D.B. and K.V.L. collected the data. C.K. and N.H. conducted the statistical analyses. D.B. and C.K. drafted the first version of the paper. All co-authors have made a substantial contribution to interpretation of the data, critically revised the article, and approved the final version, including the authorship list.

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