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ORIGINAL RESEARCH

Establishing a hepatitis C continuum of care among HIV/hepatitis C virus-coinfected individuals in EuroSIDA

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Objectives

The aim of the study was to establish a methodology for evaluating the hepatitis C continuum of care in HIV/hepatitis C virus (HCV)-coinfected individuals and to characterize the continuum in Europe on 1 January 2015, prior to widespread access to direct-acting antiviral (DAA) therapy.

Methods

Stages included in the continuum were as follows: anti-HCV antibody positive, HCV RNA tested, currently HCV RNA positive, ever HCV RNA positive, ever received HCV treatment, completed HCV treatment, follow-up HCV RNA test, and cure. Sustained virological response (SVR) could only be assessed for those with a follow-up HCV RNA test and was defined as a negative HCV RNA result measured > 12 or 24 weeks after stopping treatment.

Results

Numbers and percentages for the stages of the HCV continuum of care were as follows: anti-HCV positive (n = 5173), HCV RNA tested (4207 of 5173; 81.3%), currently HCV RNA positive (3179 of 5173; 61.5%), ever HCV RNA positive (n = 3876), initiated HCV treatment (1693 of 3876; 43.7%), completed HCV treatment (1598 of 3876; 41.2%), follow-up HCV RNA test to allow SVR assessment (1195 of 3876; 30.8%), and cure (629 of 3876; 16.2%). The proportion that achieved SVR was 52.6% (629 of 1195). There were significant differences between regions at each stage of the continuum (P < 0.0001).

Conclusions

In the proposed HCV continuum of care for HIV/HCV-coinfected individuals, we found major gaps at all stages, with almost 20% of anti-HCV-positive individuals having no documented HCV RNA test and a low proportion achieving SVR, in the pre-DAA era.

Keywords: continuum of care, Europe, HIV/HCV coinfection, sustained virological response, treatment

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Introduction

Chronic hepatitis C virus (HCV) infection is a major global health concern, with over 71 million people infected world-wide [1]. Among an estimated 14 million people living with HCV infection in the World Health Organization (WHO) European Region [1], 711 500 are also coinfected with HIV [2]. The burden of HIV/HCV coinfection is particularly high in Eastern Europe and Central Asia where injecting drug use is the main mode of HIV transmission [3]. In HIV/HCV-coinfected populations with access to combination antiretroviral therapy (cART), liver-related death has become one of the leading causes of death [4].

While the goal of HIV treatment is long-term viral suppression, HCV infection is curable. Until 2014, the standard-of-care HCV therapy was pegylated interferon (IFN) in combination with ribavirin (RIB). This resulted in cure rates, also known as sustained virological response (SVR), between 40 and 80% depending on the HCV genotype [5]. However, in HIV/HCV-coinfected individuals, treatment success was lower, ranging from 29% for genotype 1 to 62% for genotype 2/3 [6]. As a consequence of the toxicity of and contraindications for interferon (IFN)-based therapy, treatment was often not given to those most in need [7].

The introduction of new effective and well-tolerated direct-acting antivirals (DAAs) to treat HCV infection can lead to SVR in > 95% of cases [8]. While DAAs are highly efficacious, they are also very costly [5], which is currently limiting access to treatment [9]. Therefore, the benefits of the new and improved HCV treatment will not be realized unless barriers to care can be addressed.

A continuum of care (CoC) is a framework that describes the successive steps in health care required for individuals to go through to achieve optimal health outcomes [10]. The HIV continuum has become an integral public health tool for evaluating the outcome of HIV programmes, from diagnosis, to linkage to care, initiation of antiretroviral therapy and virological suppression [11,12]. The care continuum is not limited to HIV, however, and can be constructed for other conditions, such as HCV infection [10,13]. The WHO has set the goal of eliminating viral hepatitis as a public health threat by 2030 [1]. This requires a reduction in new infections by 90% and a reduction in mortality caused by viral hepatitis by 65% compared with 2015 estimates [1]. HIV/HCV-coinfected persons are considered a group with a high priority for HCV therapy [1]. Reaching this ambitious goal requires a huge effort to increase testing, linkage to care and access to effective antiviral therapy [1]. Therefore, an HCV CoC is an essential framework to predict, monitor and evaluate progress in achieving these targets and allows cross-country or population comparisons. A CoC can also be used to identify leaks/breaks in HCV care that need to be addressed in order to ensure individuals' transition through all stages and achievement of SVR. Several different HCV care continuums have been proposed for both HCV-monoinfected [13–15] and HIV/HCV-coinfected individuals [16–19]. While none of the steps in the HCV continuum of care are unique to HIV/HCV-coinfected individuals, the optimal design of a CoC might be different for coinfected individuals already linked to specialist HIV care. However, proposed continuums for coinfected individuals use diverse methodology [16,17]. More work is therefore required to develop a standardized CoC for HCV-infected people living with HIV.

The objectives of this study were therefore to establish a methodology for analysing the HCV CoC and apply it to the EuroSIDA observational HIV-infected cohort in order to identify key points of clinical HCV management in 2015 across Europe, with a focus on regional differences.

Methods

EuroSIDA study participants

EuroSIDA is a large ongoing prospective observational cohort study that began enrolling HIV-1-positive patients in 1994. There are currently data on over 22 000 HIV-positive individuals aged ≥ 16 years from 100 centres in 36 European countries, Israel and Argentina. These countries were categorized into regions, as in previous publications [20]:

- South: Greece, Israel, Italy, Portugal, Spain and Argentina.
- Central-West: Austria, Belgium, France, Germany, Luxembourg and Switzerland.
- North: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and the UK.
- Central-East: Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia and Slovenia.
- East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia and Ukraine.

To ensure that the EuroSIDA study population is representative of the current HIV-infected population in Europe, new cohorts are enrolled at regular intervals. To date, 10 patient cohorts have been recruited since 1994. For each cohort, a predefined number of patients were enrolled from each site. While individuals in cohorts 1 to 9 were enrolled irrespective of HCV status, HIV-positive

individuals in cohort 10 were also required to be anti-HCV positive (HCV RNA positive or negative). From 1 June 2014 to 31 December 2016, 4034 consecutive patients were enrolled into cohort 10. The consecutive enrolment of unselected individuals ensures that participants with irregular follow-up are not excluded from the study. Data are collected prospectively at clinical sites and sent at 12-monthly intervals (6-monthly until 2015) to the EuroSIDA coordinating centre, which is based at the Centre of Excellence for Health, Immunity and Infections (CHIP). Individuals are considered lost to follow-up (LTFU) if they do not have a CD4 count measurement, HIV RNA measurement or clinic visit for 12 months. The number of individuals LTFU annually is quite low, with Mocroft *et al.* [21] reporting the incidence of LTFU at 3.72 per 100 person-years of follow-up (PYFU), with variation across countries. If an individual has no reported data for > 1 year, the clinic is queried. If there is no record of a clinic visit by 2 and 5 years, then the clinic is queried again. Participants continue to be followed up if they transfer to another EuroSIDA clinic. Further details on the EuroSIDA cohort have been reported elsewhere [22].

Anti-HCV status and HCV RNA status have been collected since 1997, when the central plasma repository was set up which receives plasma from most individuals enrolled in EuroSIDA every 6 months. In 2006, individuals with stored plasma samples and unknown hepatitis B and C status were centrally tested for anti-HCV antibodies, HCV RNA, genotype and hepatitis B and D markers. EuroSIDA has also collected HCV treatment start and stop dates since 1997; however, since cohort 10, HCV treatment dosage, adherence, treatment-limiting adverse events, and the reason for discontinuing treatment have also been collected for HIV/HCV-coinfected individuals. Further information on the collection of anti-HCV, HCV RNA and genotype data has been detailed elsewhere [23,24].

We included all anti-HCV-positive individuals who were under follow-up (FU) on 1 January 2015 (last visit 1 January 2014 or later); the index date was defined as 1 January 2015. Baseline characteristics were defined based on the most recent measurement before the index date; individuals without a CD4 count or HIV viral load measured prior to the index date had a value up to 6 months after the index date included, if available. The most recent fibrosis marker measured prior to the index date was used to determine whether the individual had advanced fibrosis (METAVIR $\geq$ F3), which was defined using a consensus definition [25]. When more than one fibrosis marker was measured on the same day, then priority was given to a biopsy result, followed by a FibroScan result, an aspartate aminotransferase/platelet ratio index (APRI) score then finally a plasma hyaluronic acid result. Information on how fibrosis data are collected and defined in EuroSIDA has been specified elsewhere [4].

Definition of continuum of care stages

All stages of the continuum are defined in Table 1. Individuals who satisfied the inclusion criteria of being under follow-up and anti-HCV positive prior to 1 January 2015 were included in this analysis (stage 1). The number of anti-HCV-positive individuals who were HCV RNA tested before the index date (stage 2) and currently HCV RNA positive (stage 3) was then determined. Those ever HCV RNA positive prior to the index date were included in stage 4, and the proportions who initiated treatment before the index date (stage 5), completed treatment before the index date (stage 6), had a follow-up HCV RNA test after completing treatment (stage 7), and achieved cure (stage 8) were also determined. SVR could only be assessed for those with a follow-up HCV RNA test which was defined as an HCV RNA negative result measured > 12 or 24 weeks (for IFN-free or IFN-based regimens, respectively) after stopping treatment.

Depending on the denominator, the term 'cure' or 'SVR' is used in this paper. 'Cure' indicates the number of individuals with a negative HCV RNA test at > 12 or 24 weeks post-treatment among all individuals ever HCV RNA

Table 1 Hepatitis C virus (HCV) continuum of care definitions

Stage	Definition
Stage 1: anti-HCV positive	Anti-HCV antibody-positive test, HCV RNA positive, HCV genotyped or received HCV treatment before index date
Stage 2: ever HCV RNA tested	HCV RNA tested, HCV genotyped or received HCV treatment before index date
Stage 3: currently HCV RNA positive	Most recent HCV RNA test before index date was positive, HCV genotyped but not treated before index date, started treatment for the first time after index date or the first HCV RNA test result after index date is positive and never treated
Stage 4: ever HCV RNA positive	HCV-RNA-positive test, received HCV treatment or HCV genotyped before index date
Stage 5: ever received treatment	Started HCV treatment on or before index date
Stage 6: treatment completed	Completed HCV treatment on or before index date
Stage 7: FU HCV RNA available	HCV RNA test > 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively). HCV RNA test data included for duration of FU to allow for assessment of SVR
Stage 8: cured	HCV-RNA-negative test at least 12 or 24 weeks post-treatment (for IFN-free and IFN-based therapy, respectively)

FU, follow-up; IFN, interferon; SVR, sustained virological response.

positive, while 'SVR' is used to describe the same number, but among those who have received HCV treatment and have a follow-up HCV RNA test for SVR assessment.

Statistical analysis

Baseline characteristics were compared between regions using χ^2 and Kruskal–Wallis tests for categorical and continuous variables, respectively. SAS 9.4 was used for all analyses (version 9.4; SAS Institute, Cary, NC).

Results

Patient characteristics

Among 12 791 HIV-positive individuals under follow-up in EuroSIDA on 1 January 2015, 12 534 (98%) had been tested for anti-HCV, and, of them, 5173 (41%) were anti-HCV positive and included in these analyses. Of the 5173 anti-HCV-positive individuals, 1294 (25%), 1170 (23%), 679 (13%), 763 (15%) and 1267 (24%) were from Southern, Central-West, Northern, Central-East, and Eastern Europe, respectively. Overall and regional characteristics for those who were anti-HCV positive are shown in Table 2; there were significant differences between regions for all characteristics ($P < 0.001$). The overall study population was mostly male (70%), ranging from 62% male in Eastern Europe to 75% in Northern Europe. The median age was 47 years [interquartile range (IQR) 39–53 years], with a median age of 52 (IQR 47–56) years in Central-West and a younger median age of 37 (IQR 33–42) years in Eastern Europe. The most common route of HIV transmission was injecting drug use (IDU) in all regions. At least 89% of individuals in each region had an HIV viral load < 500 HIV-1 RNA copies/mL, except in Eastern Europe where only 62% of individuals were virally suppressed. The median CD4 cell count was highest in the Central-West region (593 cells/μL; IQR 409–809 cells/μL) and lowest in Eastern Europe (427 cells/μL; IQR 276–589 cells/μL).

HCV genotype and fibrosis measurement

Of the 5173 individuals who were anti-HCV positive before 1 January 2015, 4902 (94.8%) had a fibrosis marker; the most common marker was APRI score (78.9%) followed by FibroScan (18.3%), liver biopsy (2.1%) and hyaluronic acid (0.7%). Northern Europe had the lowest proportion of individuals with a fibrosis marker (83.2%), while Southern Europe had the highest (97.6%). Overall, 15.7% of those with a fibrosis marker had advanced fibrosis or cirrhosis (METAVIR ≥ F3), with the burden of ≥ F3 fibrosis ranging from 13.1% in Central-East to 17.5% in Southern Europe. Among all anti-HCV-positive individuals, 47.2% had been genotyped, with large regional differences. Genotype 1 was the most common genotype in all regions followed by genotype 3 (Table 2).

Continuum of HCV care among HIV/HCV-coinfected individuals in Europe

Of the 5173 anti-HCV-positive individuals who were included in this analysis, 4207 (81.3%) were HCV RNA tested, and 3179 (61.5%) were HCV RNA positive on the index date of 1 January 2015 (Fig. 1a). There were 3876 individuals with confirmed current or past positive HCV RNA prior to 1 January 2015, of whom 1693 (43.7%) had started HCV treatment, 1598 (41.2%) had completed HCV treatment, and 1195 (30.8%) had an HCV RNA test result after completing treatment (allowing for SVR assessment) (Fig. 1b). Although 41% of all HCV-RNA-positive individuals had completed HCV treatment, only 629 (16.2%) of the entire HCV-RNA-positive population had confirmed HCV cure. However, 403 of 1598 (25%) of all who had completed treatment had missing follow-up HCV RNA for SVR assessment. The proportion of individuals with SVR, of those who could have SVR assessed, was 52.6% (629 individuals). Of all the individuals who started HCV treatment, 84% received IFN + Ribavirin (RBV), 9% IFN + DAA regimens, and 7% IFN-free DAA regimens. The majority of individuals eligible for SVR assessment had received IFN-based regimens (95.3%), and genotypes 1 and 4 were the most common genotypes (65%).

Regional differences in the continuum of care

There were significant differences between regions at each stage of the continuum ($P < 0.0001$). The proportion of anti-HCV-positive individuals who were HCV RNA tested was > 90% in South, Central-West and Northern Europe and lower in Central-East (84.9%) and Eastern Europe (51.5%). The proportion of individuals who had not started treatment after a positive HCV RNA test result was consistently high across all regions. The proportion of ever HCV-RNA-positive individuals who completed treatment ranged from 48.4% (534 of 1103) in Southern Europe to 33.2% (211 of 635) in Eastern Europe, while the proportion of individuals who completed treatment with a follow-up HCV RNA test 12 or 24 weeks after completing treatment ranged from 65.6% (300 of 457) in Central-West to 82.8% (147 of 211) in Northern Europe. There were also large regional differences in the proportion of ever HCV-RNA-positive individuals with confirmed cure, ranging from 11.1% in Central-Eastern Europe to 19.0% in Northern and

Table 2 Characteristics of anti-hepatitis C virus (HCV)-positive individuals included in analysis overall and by region

Variable	Overall	South	Central-West	North	Central-East	East
	n (%)					
Overall	5173 (100.0)	1294 (25.0)	1170 (22.6)	679 (13.1)	763 (14.7)	1267 (24.5)
Sex						
Male	3600 (69.6)	921 (71.2)	850 (72.6)	512 (75.4)	528 (69.2)	789 (62.3)
Female	1573 (30.4)	373 (28.8)	320 (27.4)	167 (24.6)	235 (30.8)	478 (37.7)
Ethnicity						
White	4641 (89.7)	1202 (92.9)	969 (82.8)	454 (66.9)	751 (98.4)	1265 (99.8)
Fibrosis*						
< F3	4131 (84.3)	1037 (82.1)	967 (85.2)	462 (81.8)	645 (86.6)	1020 (85.4)
≥ F3[†]	771 (15.7)	226 (17.9)	168 (14.8)	103 (18.2)	100 (13.4)	174 (14.6)
HCV genotype[‡]						
1	1291 (52.8)	455 (54.7)	253 (59.1)	190 (56.7)	180 (39.6)	213 (53.9)
2	73 (3.0)	13 (1.6)	18 (4.2)	26 (7.8)	4 (0.9)	12 (3.0)
3	708 (29.0)	211 (25.4)	86 (20.1)	92 (27.5)	149 (32.8)	170 (43.0)
4	372 (15.2)	153 (18.4)	71 (16.6)	27 (8.1)	121 (26.7)	0 (0.0)
HIV risk group						
MSM	933 (18.0)	211 (16.3)	316 (27.0)	247 (36.4)	134 (17.6)	25 (2.0)
IDU	2903 (56.1)	735 (56.8)	550 (47.0)	280 (41.2)	463 (60.7)	875 (69.1)
Heterosexual	980 (18.9)	231 (17.9)	208 (17.8)	98 (14.4)	100 (13.1)	343 (27.1)
Other	160 (3.1)	32 (2.5)	65 (5.6)	30 (4.4)	28 (3.7)	5 (0.4)
HIV RNA						
< 500 copies/mL	4442 (85.9)	1238 (95.7)	1101 (94.1)	646 (95.1)	675 (88.5)	782 (61.7)
500–10 000 copies/mL	286 (5.5)	27 (2.1)	28 (2.4)	17 (2.5)	29 (3.8)	185 (14.6)
> 10 000 copies/mL	365 (7.1)	24 (1.9)	36 (3.1)	10 (1.5)	46 (6.0)	249 (19.7)
Ever received cART						
No	369 (7.1)	42 (3.2)	35 (3.0)	41 (6.0)	30 (3.9)	221 (17.4)
Yes	4804 (92.9)	1252 (96.8)	1135 (97.0)	638 (94.0)	733 (96.1)	1046 (82.6)
	Median (IQR)					
Age (years)	47 (39–53)	50 (46–54)	52 (47–56)	51 (46–56)	41 (36–48)	37 (33–42)
CD4 count (cells/μL)	530 (363–748)	577 (402–808)	593 (409–806)	550 (393–785)	536.5 (375–733)	427 (276–589)
CD4 nadir (cells/μL)	177 (76–289)	166 (70–272)	155 (56–258)	149.5 (41–240)	182 (72–295)	221 (116–335)

There was evidence of regional differences for all variables ($P < 0.0001$).
*Calculated as a proportion of those with a liver fibrosis marker; fibrosis stage was missing for 271 (5.24%) overall; 31 (11.4%), 35 (12.9%), 114 (42.1%), 18 (6.6%) and 73 (26.9%) in South, Central-West, North, Central-East and Eastern Europe, respectively ($P < 0.0001$). [†]Either a biopsy (≥ METAVIR stage F3), FibroScan (> 9.5 kPa), APRI (score > 1.5) [25] or hyaluronic acid level (> 160 ng/mL) [26] during follow-up. [‡]Calculated as a proportion of those genotyped; genotype was missing for 2729 (52.8%) overall; 462 (16.9%), 742 (27.2%), 344 (12.6%), 309 (11.3%) and 872 (32.0%) in South, Central-West, North, Central-East and Eastern Europe, respectively ($P < 0.0001$).
cART, combination antiretroviral therapy; IDU, injecting drug use; MSM, men who have sex with men; APRI, aspartate aminotransferase/platelet ratio index.

Southern Europe. Among individuals cured, Northern Europe also had the highest proportion of individuals who had received DAA (IFN-free) treatment (15%). No individuals in Central-East or Eastern Europe received IFN-free regimens.

Discussion

We propose an eight-stage HCV CoC for HIV/HCV-coinfected individuals, which would allow cross-study comparisons for access and outcomes of HCV treatment in HIV/HCV-coinfected individuals. This tool will allow the assessment of improvements in services over time and highlight gaps where individuals are not accessing appropriate care.

Lourenço *et al.* [27] make the case for a standardized HIV continuum based on inconsistencies found in continuums from the USA, Canada (British Columbia), France and Denmark. For example, while all reported viral suppression, the definitions varied greatly, meaning that cross-study comparisons, an essential tool for monitoring, were not feasible [27]. The differences highlight the importance of a standardized continuum if comparisons with different populations and time-points are to be made confidently or if the impact of public health programmes is to be measured [27]. While this point was emphasized for the HIV continuum, it also stands in the HCV context. Although we defined eight stages in this continuum, more or fewer stages could be included depending on the setting. However, it is important to ensure that key indicators around diagnosis, treatment and cure are included to monitor progress towards the WHO 2030 goals for elimination of viral hepatitis as a public health threat [1]. As well as not estimating the undiagnosed population, we did not include an accurate measure of 'engagement in care,' which other HIV/HCV-coinfection continuums have estimated [18]. This would be helpful to understand

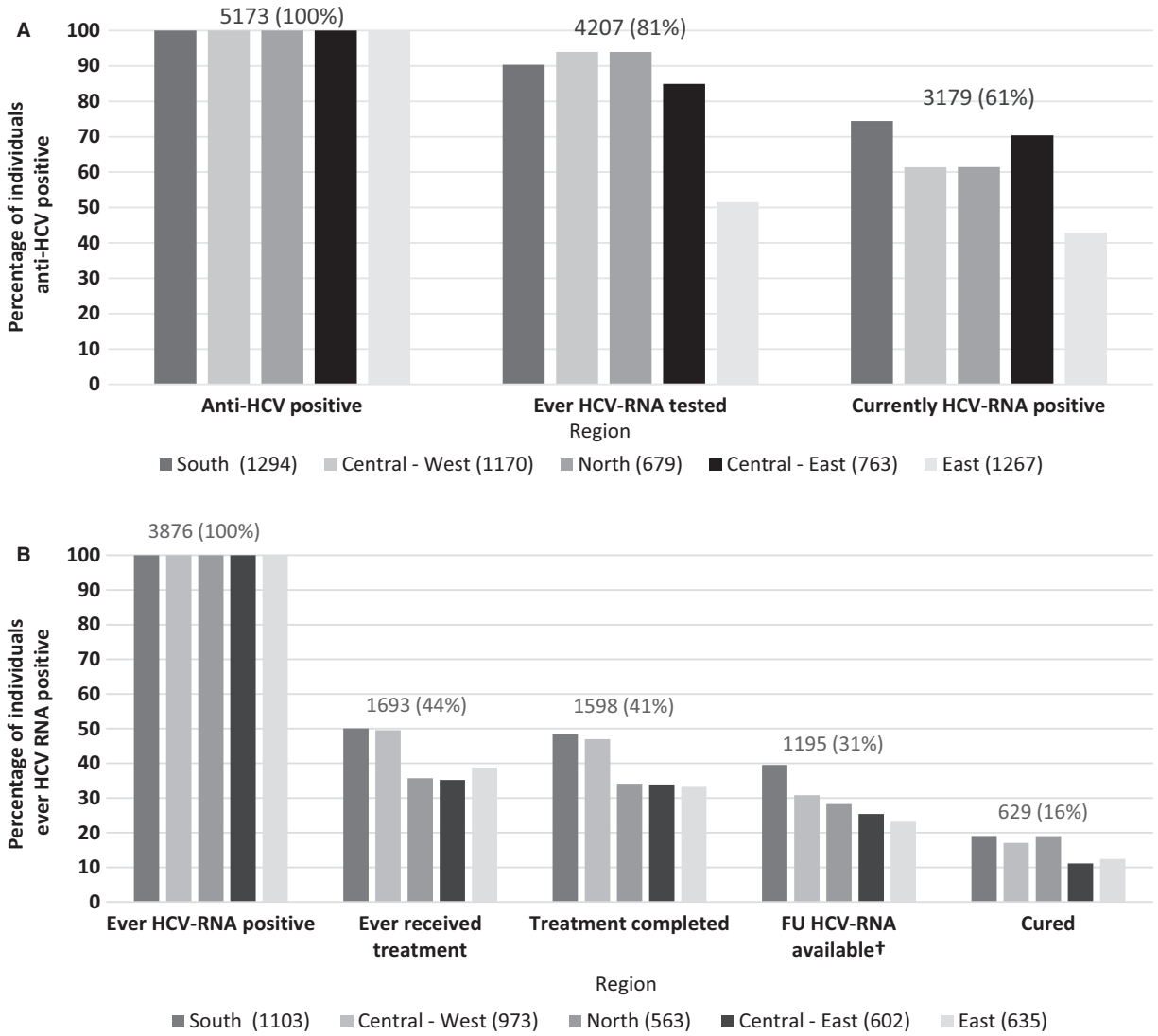

Fig. 1 Hepatitis C virus (HCV) continuum of care, by region. The figure shows the diagnostic (a) and treatment (b) stages of the continuum of HCV care among HIV/HCV-coinfected individuals in different geographical regions of Europe. Overall values for each stage of the continuum are shown above each stage, with percentages in parentheses. The χ^2 test provides evidence of regional difference at all stages ($P < 0.0001$). †Individuals who had an follow-up (FU) HCV RNA test at least 12 or 24 weeks after completing treatment for interferon (IFN)-free and IFN-based therapy, respectively.

whether patients are not transitioning through the stages because of a lack of engagement or failures in health structures so that interventions and resources can be targeted at the appropriate area.

Other descriptions of HCV continuums included information that we did not. For example, Hajarizadeh *et al.* [13] included an estimate for the number of people living with HCV in Australia and were therefore able to provide an estimate of the proportion of individuals living with HCV who were undiagnosed (25%). However, they did not include information on individuals' engagement in care [13]. The Austrian HIV Cohorts Study developed a continuum with similar stages to the continuum presented in this paper [19]. While they also did not estimate the number of people living with HCV, their definition of SVR allowed them to capture reinfections, which we did not [19]. Cachay *et al.* [17] included stages in their continuum around engagement in care; however, as their continuum is based on data from a single clinic, they also did not include an estimate of the number of people living with HCV. However, our proposed continuum has some advantages over other descriptions of the HCV CoC,

such as including information on the proportion of individuals that completed HCV treatment and the proportion of individuals who were followed up after stopping treatment, which provides insight into whether lack of engagement with care is a potential reason for not achieving SVR.

In our patient population of 5173 individuals coinfected with HIV and HCV from across Europe, there were major gaps at all stages of our suggested hepatitis C CoC at 1 January 2015, with significant disparities between the different regions in Europe at each stage. Approximately 1 in 5 of those anti-HCV positive had no documented HCV RNA test. Less than half of those chronically infected had initiated anti-HCV therapy and only 16.2% had a documented HCV cure, which is partly attributable to the lack of effective HCV therapy available at the time. The proportion of individuals who were HCV RNA tested varied greatly between regions. An HCV RNA test is relatively expensive [28], and it is possible that in some settings HCV RNA testing is primarily targeted at individuals where HCV treatment is considered.

Among patients known to be HCV RNA positive, the proportion who had received HCV treatment was highest in Southern and Central-Western Europe and lower in other regions. Although the proportion treated in Northern Europe was similar to that in Central-East and Eastern Europe, fewer people had been HCV RNA tested in Central-East and Eastern Europe. Although we have focused on which stages might be needed in a hepatitis C continuum, it is worth noting that, for descriptive purposes, this continuum is based on January 2015, before the widespread introduction of DAAs. In the interferon era, therapy was often deferred because of contraindications, toxicities, low efficacy and the cost associated with IFN-based therapy [29]. Alcohol consumption, current IDU and having a pre-existing mental illness have been identified as the main reasons for not initiating HCV treatment; however, there is a lack of evidence to support excluding patients for these reasons, with treatment adherence better predicting SVR [30]. However, there are still challenges in the DAA era; while The European Association for the Study of the Liver (EASL) guidelines for treating HCV infection recommend the prioritization of HCV therapy for those with advanced liver fibrosis or from high-risk groups [31], access to treatment is still low because of high drug prices.

The proportion of individuals with a confirmed HCV cure was low across all regions. These low cure rates should also be viewed in the context that IFN plus RBV was the predominant regimen in this study and that the majority of the study population had genotype 1 or 4, which are difficult to cure genotypes with IFN-based regimens [32]. At the point of analysis, second-generation DAAs had only been available for a short time, and therefore DAA uptake was still low. Only 56 (4.7%) of the 1195 individuals with a follow-up HCV RNA test after completing treatment received IFN-free treatment. Nonetheless, we have already seen a rapid increase in DAA uptake in 2014 and 2015 for all EuroSIDA regions except Eastern Europe [33]. As DAAs are highly effective for all genotypes [8], we expect to see SVR rates improving in the DAA era.

One of the main limitations of the study was the lack of a follow-up HCV RNA measurement at least 12/24 weeks after completing treatment, making it was impossible to determine SVR for all patients. It is possible that HCV RNA had been measured at a site other than an HIV clinic and therefore not reported, although substantial efforts have been made to follow up missing data from all sites as part of the quality assurance programme in EuroSIDA. There were also insufficient data on date of HCV diagnosis, meaning that it was not possible to look at late presentation in our analysis. Although cohorts are more inclusive and allow more generalizable findings than clinical trial populations [34], they are still not entirely representative of all HCV-infected individuals as there are vulnerable groups or incarcerated populations that are not included in cohorts. This study did not estimate the undiagnosed population, which is an important part of the continuum as one of the major breakpoints of the HCV continuum is diagnosis. Our study also has a number of important strengths, such as being one of the first studies to suggest a comprehensive CoC for HCV- and HIV-coinfected individuals. The size of the study population, which includes data from clinics all over Europe, is also a strength, as other continuums only include data from a single site, making the results less generalizable.

The method we propose for the HCV continuum was applied to the IFN era and will allow us to evaluate the effect of DAA therapy on transition through care at a later date. The gaps and regional differences identified emphasize the importance of assessing the treatment landscape, developing strategies to reduce prevalence, and establishing better standards of care for individuals with both HIV and HCV infections, as well as emphasizing the importance of in-depth analyses of the reasons for these gaps at the local level. The majority of coinfected individuals are injecting drug users [1], which means that they also face social issues such as stigma and marginalization which act as barriers to care [35]. Therefore, work on removing barriers to care and establishing a meaningful continuum is essential if the goal of eliminating viral hepatitis as a public health threat by 2030 [1] is to be met.

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SA, LP, JKR, JDL and AM conceived the project, designed the analysis, interpreted the findings, and conceptualized the main messages. SA executed the analysis and wrote and revised the first and subsequent drafts of the manuscript. LP and AM reviewed and commented on the first and subsequent drafts of the manuscript. MS, AY, AS, PD, JG, JV, MG, RF, SB, MR, CL, EJ, GW, HS, KF, ADM and AH reviewed and commented on the final draft of the manuscript and were involved in the interpretation of findings.

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