Establishing a hepatitis C continuum of care among HIV/HCV co-infected individuals in EuroSIDA

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Word count: 3500
Abstract word count: 210

Keywords: Continuum of care, HIV/HCV co-infection, Europe, Treatment, SVR

Abstract

Objectives: To establish a methodology for evaluating the hepatitis C continuum of care in HIV/HCV co-infected individuals and to characterise the continuum in Europe on 1/1/2015, prior to widespread access to direct-acting antiviral (DAA) therapy.

Methods: Stages included in the continuum were: 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 virologic 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 more than 12 or 24 weeks after stopping treatment.

Results: Following stages of the HCV continuum of care were defined: anti-HCV positive (n=5173), HCV-RNA tested (4207/5173; 81.3%), currently HCV-RNA positive (3179/5173; 61.5%), ever HCV-RNA positive (n=3876), initiated HCV treatment (1693/3876; 43.7%), completed HCV treatment (1598/3876; 41.2%), follow-up HCV-RNA test to allow SVR assessment (1195/3876; 30.8%), and cure (629/3876; 16.2%). The proportion that achieved SVR was 52.6% (629/1195). 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 co-infected 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.

Introduction

Chronic hepatitis C virus (HCV) infection is a major global health concern, with over 71 million people infected worldwide (1). Among an estimated 14 million people living with HCV infection in the World Health Organization (WHO) European Region (1), 711500 are also co-infected with HIV (2). The burden of HIV/HCV co-infection is particularly high in Eastern Europe and Central Asia where injection drug use is the main mode of HIV transmission (3). In HIV/HCV co-infected 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 is a curable infection. 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 virologic response (SVR), between 40%-80% depending on HCV genotype (5). However in HIV/HCV co-infected individuals treatment success was lower, ranging from 29% for genotype 1 and 62% in genotype 2/3 (6). Due to the toxicity and contraindications to 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 can lead to SVR in more than 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 realised unless barriers to care can be addressed.

A continuum of care (CoC) is a framework that describes the successive steps in healthcare 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 (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 due to viral hepatitis by 65% compared with 2015 estimates (1). HIV/HCV co-infected persons are considered a group with high priority of HCV therapy (1). Reaching this ambitious goal requires a huge effort to increase testing, linkage to care and access to effective anti-viral 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 achieve SVR. Several different HCV care continuums have been proposed for both HCV mono-infected (13–15) and HIV/HCV co-infected individuals (16–19). While none of the steps in the HCV continuum of care are unique to HIV/HCV co-infected individuals, the optimal design of a continuum of care might be different for co-infected individuals already linked to specialist HIV care. However, proposed continuums for co-infected individuals are using diverse methodology, (16,17). More work is therefore required to develop a standardised continuum of care for HCV infected people living with HIV.

The objectives of this study were therefore to establish a methodology for analysing the HCV continuum of care, and apply it to the EuroSIDA observational HIV 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 22000 HIV-positive individuals aged 16 or older from 100 centres in 36 European countries, Israel and Argentina. These countries were categorised into regions of Europe, as in previous publications (20):

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

To ensure the EuroSIDA study population is representative of the current HIV 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 cohort one to nine were enrolled irrespective of HCV status, HIV positive individuals in cohort ten were also required to be anti-HCV positive (HCV-RNA positive or

negative). From June 1st 2014 until December 31st 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 to the EuroSIDA coordinating centre at 12-monthly intervals (6 monthly until 2015) intervals, 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 reporting the incidence of LTFU at 3.72 per 100 person years of follow-up (PYFU), with variation across countries (21). If an individual has no reported data for more than one 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 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 six months. In 2006 individuals with stored plasma samples and unknown hepatitis B & 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 date since 1997; however, since cohort 10, HCV treatment dosage, adherence, treatment-limiting adverse events, and the reason for discontinuing treatment has also been collected for HIV/HCV co-infected 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) at 1/1/2015 (last visit 1/1/2014 or later), the index date was defined as 1/1/2015. 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 ≥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 APRI score then finally a plasma hyaluronic acid result. Information on how fibrosis data is 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 that satisfied the inclusion criteria of being under follow-up and anti-HCV positive prior to 1/1/2015 were included in this analysis (stage 1). The number of anti-HCV positive individuals that 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, the proportion of whom 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) was 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 more than 12 or 24 weeks (for IFN-free or IFN based regimens respectively) after stopping treatment.

Depending on the denominator, the term ‘cure’ or ‘SVR’ was used in this manuscript. Cure indicates the number of individuals with a negative HCV-RNA test at more than 12 or 24 weeks post-treatment among all individuals ever HCV-RNA positive, while SVR is used to describe the same number, however, among those that have received HCV treatment and have a follow-up HCV-RNA test for SVR assessment.

Table 1: 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 more than 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)

Statistical analysis

Baseline characteristics were compared between regions using chi-squared and Kruskal-Wallis tests for categorical and continuous variables respectively. SAS 9.4 was used for all analysis (version 9.4; SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

Among 12791 HIV positive individuals under follow-up in EuroSIDA at 1/1/2015, 12534 (98%) had been tested for anti-HCV, and among 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 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% in Eastern Europe to 75% in Northern Europe. The median age was 47 years old (interquartile range [IQR]: 39-53), with a median age of 52 (IQR: 47-56) in Central-West and a younger median age of 37 (IQR: 33-42) in Eastern Europe. The most common route of HIV transmission was injection drug use (IDU) in all regions. At least 89% of individuals in each region had an HIV viral load <500 copies per ml (cp/ml), except in Eastern Europe where only 62% of individuals were virally suppressed. The median CD4 cell count was highest in Central-West (593 cells/mm^3 IQR: 409-809) and lowest in Eastern Europe (427 cells/mm^3 IQR: 276-589).

HCV genotype and fibrosis measurement

Of the 5173 individuals that were anti-HCV positive before 1/1/2015, 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, 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).

Table 2: Characteristics of anti-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)
	Hetero	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 (cp/ml)	**<500**	4442 (85.9)	1238 (95.7)	1101 (94.1)	646 (95.1)	675 (88.5)	782 (61.7)
	500-10000	286 (5.5)	27 (2.1)	28 (2.4)	17 (2.5)	29 (3.8)	185 (14.6)
	>10000	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		47 (39-53)	50 (46-54)	52 (47-56)	51 (46-56)	41 (36-48)	37 (33-42)
CD4 count (cells/mm^3)		530 (363-748)	577 (402-808)	593 (409-806)	550 (393-785)	536.5 (375-733)	427 (276-589)
CD4 nadir (cells/mm^3)		177 (76-289)	166 (70-272)	155 (56-258)	149.5 (41-240)	182 (72-295)	221 (116-335)

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 (>9.5kPa), APRI (score >1.5) (25), or hyaluronic acid (>160ng/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)

Continuum of HCV care among HIV/HCV co-infected individuals in Europe

Of the 5173 anti-HCV positive individuals that were included in this analysis, 4207 (81.3%) were HCV-RNA tested, and 3179 (61.5%) were HCV-RNA positive at the index date 1/1/2015 (Figure 1). There were 3876 individuals with confirmed current or past positive HCV-RNA prior to 1/1/2015, among which 1693 (43.7%) had started HCV treatment, 1598 (41.2%) had completed HCV treatment, 1195 (30.8%) had an HCV-RNA test result after completing treatment (allowing for SVR assessment) (Figure 2). 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, 403/1598 (25%) of all who had completed treatment had missing follow-up HCV-RNA for SVR assessment. The proportion of individuals with SVR, of those that could have SVR assessed, was 52.6% (629 individuals). Of all the individuals that started HCV treatment, 84% received IFN+RBV, 9% IFN+DAA regimens, and 7% received IFN-free DAA regimens (Table 3). The majority of individuals eligible for SVR assessment had received interferon-based regimens (95.3%) and genotype 1 or 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 that 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 that 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 that completed treatment ranged from 48.4% (534/1103) in Southern Europe to 33.2% (211/635) in Eastern Europe, while the proportion of individuals that completed treatment with a follow-up HCV-RNA test 12 or 24 weeks after completing treatment ranged from 65.6% (300/457)

in Central-West to 82.8% (147/211) 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 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.

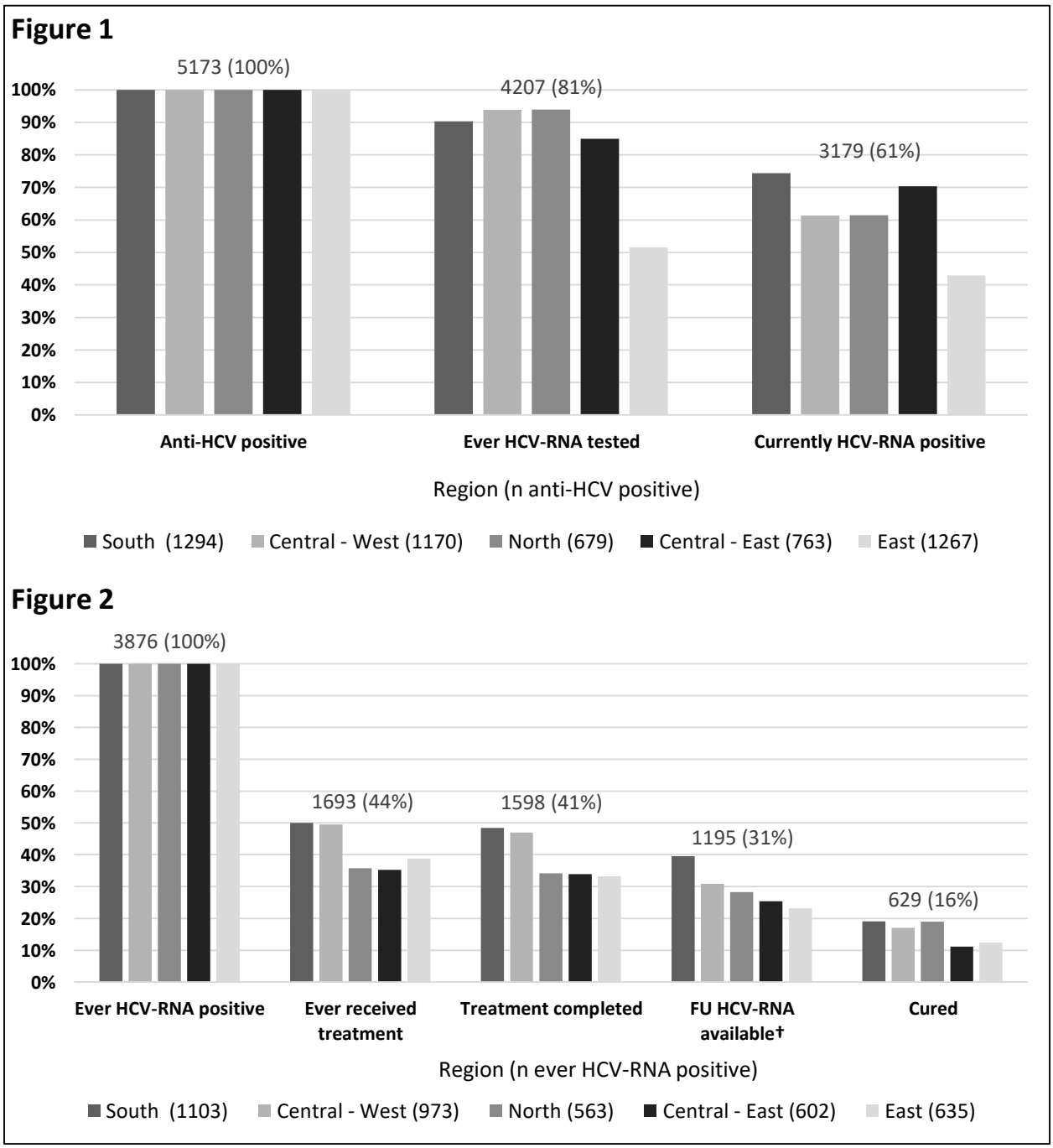

Figure 1 and 2: HCV continuum of care, by region. The figure shows the diagnostic (Figure 1) and treatment (Figure 2) stages of the continuum of HCV care among HIV/HCV co-infected individuals in different geographical regions of Europe. Overall values for each stage of the continuum are shown above each stage, with percentages in parenthesis. Chi-squared test provides evidence of regional difference at all stages ($p<0.0001$)
†Individuals that had a FU HCV-RNA test at least 12 or 24 weeks after completing treatment (for IFN-free and IFN-based therapy, respectively.

Discussion

We propose an eight stage HCV continuum of care for HIV/HCV co-infected individuals, which would allow cross-study comparisons for access and outcomes of HCV treatment in HIV/HCV co-infected 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 make the case for a standardised HIV continuum based on inconsistencies found in continuums from the USA, Canada (British Columbia), France, and Denmark (27). For example, while all reported viral suppression, the definitions varied greatly meaning cross-study comparisons, an essential tool for monitoring, were not feasible (27). The differences highlight the importance of a standardised continuum if comparisons with different populations and time-points are to be made confidently or if the impact of public health programs are to be measured (27). While this point was emphasised in 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 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 co-infection continuums have estimated (18). This would be helpful to understand whether patients are not transitioning through the stages due to 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. include 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 that were undiagnosed (25%) (13). 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. 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 (17). 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 potential reasons for not achieving SVR.

In our patient population of 5173 individuals co-infected with HIV and hepatitis C from across Europe, there were major gaps at all stages of our suggested hepatitis C continuum of care 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 that 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 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 at January 2015, before the widespread introduction of DAAs. In the interferon era, therapy was often deferred due to contraindications, toxicities, low efficacy and the cost associated with interferon-based therapy (29). Alcohol consumption, current injecting drug use 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 recommend the prioritisation of HCV therapy for those with advanced liver fibrosis or from high-risk groups (31), access to treatment is still low due to high drug prices.

The proportion of individuals with 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 has been measured at a different site than HIV clinics tests and therefore not reported, although substantial efforts have been made to follow-up missing data from all sites as part of the QA program in EuroSIDA. There was also insufficient data on date of HCV diagnosis, meaning it was not possible to look at late presentation in our analysis. Although cohorts are more inclusive and generalisable than clinical trials (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 continuum of care for HCV and HIV co-infected 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 generalisable.

The method we propose for the HCV continuum was applied to the interferon 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 emphasise 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, as well as emphasising the importance of in-depth analyses of the reasons for these gaps at the local level. The majority of co-infected individuals are injecting drug users (1), which means they also face social issues such as stigma and marginalisation 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.

Acknowledgements

SA, LP, JKR, JDL and AM conceived the project, designed the analysis, interpreted the findings, and conceptualised 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.

The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

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Funding:

EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under **EuroCoord** grant agreement n° 260694. Current support includes unrestricted grants by ViiV Healthcare LLC, GlaxoSmithKline R&D Limited, Janssen Scientific Affairs, Janssen R&D, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Gilead Sciences. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 148522). The study is also supported by a grant [grant number DNRF126] from the **Danish National Research Foundation** and by the International Cohort Consortium of Infectious Disease (RESPOND).

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