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Title: Uptake of HCV treatment in HIV/HCV coinfected patients across Europe in the era of direct-acting antivirals

Running head: Uptake of DAA in HIV/HCV patients

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Introduction

The first oral direct-acting antivirals (DAAs) for treatment of hepatitis C virus (HCV) infection, the protease inhibitors telaprevir and boceprevir, were approved in 2011 [1]. Their antiviral efficacy was limited and they had to be combined with pegylated interferon (IFN) and ribavirin (RBV) and were associated with a high risk of serious adverse effects [2, 3]. The next generation of more potent and better tolerated DAAs was approved by the European Medicines Agency in 2014, and includes the polymerase inhibitor sofosbuvir, the NS5A replication complex inhibitor daclatasvir, and the protease inhibitor simeprevir [4]. Since then, additional DAAs from different drug classes have been approved [4]. INF-free DAA combination therapy is now considered the standard of care for treatment of chronic hepatitis C, and DAAs are included in the WHO list of essential medicines [5]. HCV cure rates greater than 95% have been reported with similar treatment outcomes in both HCV mono-infected and HIV/HCV co-infected individuals [6]. Due to the negative impact of immunosuppression on progression of liver fibrosis, HIV/HCV co-infected individuals are considered a group with high priority of HCV therapy [7]. However, the high market price of branded DAAs limits the access to this treatment even among some high-income countries [8]. Furthermore, there is a high variability in market prices for DAAs, particularly in high-income countries, with little correlation between drug prices and gross national income [9]. Although a marked increase since 2014 in uptake of DAAs among HIV/HCV individuals in Europe is anticipated, their use is expected to vary significantly across Europe, reflecting differences in affordability and prioritization within the healthcare systems as well as differences in the burden of liver fibrosis across Europe. In some countries and particular patient groups, IFN-based therapy might still be used. The aim of this study was to investigate

regional differences in the rate of HCV treatment uptake, and type of therapy used among HIV/HCV co-infected patients in the pan-European EuroSIDA study after 2011.

METHODS

Study population and data collection

Patients were included from the EuroSIDA study, a large prospective observational cohort of more than 22000 HIV-1 positive patients followed in 100 hospitals in 35 European countries plus Israel and Argentina [10]. Patients were enrolled into ten cohorts from 1994 onward. In cohort 1-9, consecutive HIV positive patients older than 16 years of age were enrolled irrespective of HCV status. In cohort ten all HIV positive patients were also required to be positive for anti-HCV antibodies (HCV-RNA positive or negative). At recruitment, in addition to demographic and clinical data, a complete ART history is obtained together with the most recent CD4 cell counts and HIV-RNA measurements, as well as anti-HCV, HCV-RNA, HCV genotype, hepatitis B surface antigen (HBsAg) and HBV-DNA. Data is collected prospectively at clinical sites and sent to the coordinating centre at 6 monthly intervals. At each follow-up visit, all CD4 cell counts, HIV-RNA, anti-HCV, HCV-RNA, genotype, HBsAg and HBV-DNA results measured since last follow-up are collected, and the start and stop dates for antiretroviral drugs and HCV and HBV drugs. Detailed information about data collected in EuroSIDA can be found at http://www.chip.dk/Ongoing-Studies/EuroSIDA/About.

All HCV-RNA positive patients, with prospective follow up after January 1 2011 (when the first DAAs were introduced) were eligible for this study. Median last follow up date was June 2016.

Classification of liver fibrosis stage

Liver fibrosis stage, according to the METAVIR classification [11], was defined using data from liver biopsies, fibroscan, the aspartate aminotransferase to platelet ratio index (APRI) or from plasma hyaluronic acid, as previously described [12]. F4 fibrosis was defined from validated liver biopsy, fibroscan measurements greater than 12.5 kPa, an APRI score >2 and hyaluronic acid measurements >250 ng/ml. Fibrosis values at any given time point were the last values measured before the time point in question and where more than one measurement of fibrosis was recorded on the same date, the biopsy was assumed to be the gold standard, followed by fibroscan, APRI then hyaluronic acid.

HCV treatment categories

HCV treatment regimens were divided into three categories. 1) IFN +/- RBV (no DAA), 2) DAA+IFN +/- RBV, 3) DAA +/- RBV (no IFN).

Statistical analysis

Baseline was defined as the latest of 1 January 2011, recruitment to EuroSIDA, or testing HCV-RNA positive. Regions of Europe were classified as in previous studies [13]. Based on country of residence, people were grouped into five regions: West: Austria, Belgium, France, Germany, Luxembourg, Switzerland. South: Argentina, Greece, Israel, Italy, Portugal, Spain. North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom. East Central: Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia. East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Slovakia, Ukraine.

Characteristics at last visit for those not starting HCV treatment during follow up were compared to the characteristics at starting HCV treatment for those who started treatment during prospective follow-up. In those HCV-RNA positive, we calculated the incidence rate (IR) per 1000 person years of follow-up (PYFU) for 1) starting any HCV treatment during follow-up and 2) starting IFN-free DAA therapy. This analysis included follow up from baseline until last visit or first starting HCV treatment; patients may have been exposed to HCV treatment prior to baseline.

Poisson regression was used to determine the factors associated with starting IFN-free DAA during prospective follow-up. CD4 count , HIV viral load, starting combination antiretroviral therapy (cART), starting IFN/RBV only treatment, AIDS diagnosis, diagnosis of AIDS within the last 12 months (recent AIDS), fibrosis stage, HCV-RNA level, and HBsAg status were included as time-updated variables. Other factors were fixed at baseline (gender, age, ethnic group, HIV transmission route, prior HCV treatment and CD4 nadir). All variables were included in multivariate models. In the Poisson regression model, Argentina was combined with Southern Europe, and 2011 and 2012 were combined as they had very similar incidence rate ratios of starting HCV treatment. HIV viral load was categorised as <500 and ≥500. CD4 count was analysed as two categories (≤350 and >350). Neither prior AIDS nor recent AIDS was associated with starting DAA and therefore only prior AIDS was included in the final multivariate model.

All analyses were performed using SAS version 9.4 (Statistical Analysis Software, Cary, NC, US).

RESULTS

Incidence of starting any HCV therapy

A total of 4308 HCV-RNA+ HIV positive persons were included in the study. Among included persons, 1255 (29.1%) were from Southern Europe and Argentina, while 970 (22.5%), 663 (15.4%), 633 (14.7%), and 787 (18.3%) were from West, North, Central East and East, respectively. During 11863 PYFU, a median of 2.0 years per person (IQR 1.0–4.7), 1113 (25.8%) started any HCV therapy (incidence 93.8/1000 PYFU; 95%CI 88.3–99.3). The incidence of starting therapy remained stable between 2011 (55.4/1000 PYFU; 95% CI 44.1–66.7) and 2014 (65.0/1000 PYFU; 95% CI 53.3–76.7), but increased sharply in 2015 (166.7/1000 PYFU; 95%CI 151.2-182.3) and 2016 (150.5/1000 PYFU; 95% CI 132.9–168.1).

Patient characteristics at time of starting HCV therapy

Table 1 shows the patient characteristics at time of starting any HCV treatment compared with last clinic visit in those untreated during follow up. The median age of treated and untreated was 47 and 45 years, respectively, and around a third of all patients were HCV treatment experienced. Compared with untreated, HCV treated patients were less likely to be female (23% vs. 30%), come from Central East (10% vs. 16%) and East (12% vs. 21%) and have a history of injection drug use (54% vs. 60%), but more likely to have genotype 1 (44% vs. 39%) and cirrhosis (22% vs. 11%). Treated persons were slightly more likely to have suppressed HIV-RNA (93% vs. 89%) whereas the median (IQR) CD4 count was similar [570 cells/mm^3 (401–770) vs. 548 cells/mm^3 (364–773)]. The proportion of untreated patients with ≥F3 was similar when comparing South (54%) with West (52%) and North (50%), but substantially lower than in Central East (86%) and East (79%).

Use of different HCV treatment regimens

Figure 1 shows the use of IFN-based and INF-free regimens between 2011 and 2016, stratified by region. In 2015 and 2016, almost 90% of persons starting HCV therapy received an IFN-free regimen (n=638/722; 88.4%), ranging from 38/61 (62.3%) in East to 249/258 (96.5%) in South/Argentina. Use of IFN+RBV in all regions in 2015 and 2016 was restricted to a few countries. In 2015/2016, 66/722 (9.1%) persons from 16 different countries in all EuroSIDA regions started IFN+RBV. In South, all who started IFN+RBV in 2015/2016 were genotype 1, while in other regions those starting IFN+RBV were from all genotypes. In Central East IFN-based treatment was used exclusively until 2015. In 2015 and 2016 IFN-free regimens were used in 60% and 80% of treatments in Central East, respectively. In East, uptake of HCV therapy was generally low in the entire study period and dominated by IFN+RBV, although IFN-free therapy was used in almost 90% of those starting HCV treatment in 2016. Among 638 persons starting INF-free treatment in 2015 and 2016, the most commonly used regimen was sofosbuvir/ledipasvir +/- RBV (n=328, 51.4%) followed by ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- RBV (n=128, 20.1%) and sofosbuvir/daclatasvir +/- RBV (n=108, 16.9%).

Incidence of starting IFN-free DAA HCV treatment

638 (14.8%) persons started an IFN-free DAA regimen during 13043 PYFU (median follow-up 2.3 years; IQR 1.3–5.1 years) with an overall incidence of 56.0/1000 PYFU (95% CI 51.9–60.0). The incidence of starting IFN-free DAA increased from 7.8/1000 PYFU (5.9–9.8) in 2014 or earlier to 135.2/1000 PYFU (122.0–148.5) in 2015 and 128.9/1000 PYFU in 2016 (113.5–144.3), and varied significantly across regions (figure 2). The increase was highest in North and West and intermediate in South. From 2015 to 2016, the incidence decreased by 46% in South,

whereas the incidence continued to increase in West and North. In both Central East and East there was a modest increase in incidence in use of DAAs in 2015 and 2016.

Within each region the uptake of IFN-free DAA varied substantially (figure 3). For example in West, which included six countries each with at least 30 persons under follow up in 2016, the use of DAA therapy varied from 4% to 62%. In East, uptake of DAA was less than 5% in four out of six countries. A notable exception is Georgia where 31% have been treated with DAAs as part of a national hepatitis C elimination program paid for by Gilead Sciences [14]. Among the 16 countries which according to the study by Marshall et al [8] had no restrictions for reimbursement of IFN-free DAA based on both fibrosis stage and recent drug/alcohol dependence or that prioritized those HIV/HCV co-infected, the uptake of IFN-free DAA among persons under follow up in 2016 was only 22.2% in all countries combined, and exceeded 40% in just four countries (France, Iceland, Netherlands and Slovenia).

Factors associated with starting IFN-free DAA treatment

Figure 4 shows the adjusted incidence rate ratios of starting IFN-free DAA treatment during follow up. Females were less likely to start IFN-free DAA treatment [incidence rate ratio, IRR: 0.77 (95% confidence interval, CI 0.63–0.93)], as were individuals from Central East (IRR 0.41, 95% CI 0.29–0.56) vs. South, or East (IRR 0.47, 95% CI 0.32–0.68) vs. South. Persons with a history of injecting drug use (IDU) were less likely than non-IDU to start DAA (IRR 0.84, 95% CI 0.68–1.02), but the result did not reach statistical significance (p=0.080). HCV genotype 3 (IRR 0.58, 95% CI 0.46–0.74) vs. genotype 1, and those who had not started cART (IRR 0.65, 95% CI 0.49–0.87) vs. on cART and those with detectable HIV-RNA (IRR 0.44, 95% CI 0.29 – 0.67) were also less likely to start DAA treatment. In contrast, older persons (IRR 1.18, 95% CI

1.07–1.30) per 10 years older, those with HCV-RNA >500.000 IU/ml (IRR 1.28, 95% CI 1.08–1.51) vs. ≤500.000 IU/ml and those with cirrhosis (IRR 4.40, 95% CI 3.63–5.33) vs. F0/F1, were more likely to start DAA. After adjustment, there was no difference in the incidence of starting DAA-based HCV treatment comparing 2016 with 2015 (IRR 1.05, 95% CI 0.89–1.23; p=0.55). The gender effect was consistent across regions (p-value=0.51 for interaction between region and gender for starting IFN-free DAA), but was most pronounced in those younger than 35 years of age (IRR 0.20, 95% CI 0.055–0.73, p=0.015), while for those aged 35–50 and >50, there was a much smaller difference (IRR 0.79, 95% CI 0.61-1.01, p=0.061 and 0.78, 95% CI 0.57–1.06, p=0.11 respectively, p=0.0001 for interaction between age and gender). Adding type of cART regimen to the model showed that receiving an integrase inhibitor based regimen (compared with not receiving cART) was associated with a higher incidence of starting IFN-free DAA (IRR 1.85, 95% CI 1.16–2.94), whereas both protease inhibitor and non-nucleotide reverse transcriptase inhibitor regimens were not (p>0.6).

We performed a number of sensitivity analyses, restricting included patients to either those with F3 or F4 fibrosis at baseline, or those with a history of IDU, or excluding men who have sex with men, or including only countries with no restrictions for reimbursement according to Marshall et al [8]. In adjusted analysis, factors associated with starting IFN-free DAA therapy were very consistent and similar to the findings in the general analysis, although not all differences were statistically significant due to the reduced power of this analysis (results not shown). The only exceptions were that not receiving cART was no longer associated with starting IFN-free DAA in an adjusted analysis including only IDU (IRR 1.05, 95% CI 0.69-1.59, p=0.835), and adjusted analysis including only countries with no reimbursement restrictions showed the incidence of starting IFN-free DAA was lower in 2016 compared with 2015 (IRR 0.77, 95% CI 0.63–0.94,

p=0.0089). The IRR for comparing females with males was similar in all sensitivity analyses with the point estimate ranging from 0.77-0.87.

DISCUSSION

Among 4308 HIV/HCV co-infected persons followed in 35 European countries as well as Israel and Argentina, 26% started anti-HCV therapy between 2011 and 2016. The overall incidence of starting therapy remained relatively stable until 2014, but increased markedly in 2015. By 2014 IFN-free DAA therapy was the predominant anti-HCV regimen used in Western Europe. The uptake of IFN-free treatment did not start to pick up until 2015 in Central East and East, and remained significantly lower than in the other regions.

Since effective cART against HIV infection became available 20 years ago, its uptake has been lower in Eastern Europe compared with Western Europe [15]. History is now repeating itself with regards to effective and well-tolerated anti-HCV therapy. Although several DAAs have been granted market authorization in the countries in East, prescription of the drugs are restricted by their high prices and lower purchasing power in this part of Europe [16]. Both Gilead Sciences [17] and Bristol-Myers Squibb [18] have signed license agreements that allow generic manufacturing of sofosbuvir/ledipasvir and daclatasvir for sale in more than 100 low- and middle income countries. However, among the countries in the EuroSIDA East region none are included in the access plans. Hence, HCV infected persons in general from this region have very limited access to DAAs via their healthcare system. The more affluent patients will be able to get DAAs outside the national healthcare system by buying generic DAAs directly from other countries or from buying them on the internet. One notable exception is Georgia that since April 2015 has had a national hepatitis C elimination program where all HCV infected persons are offered DAA

therapy paid for by Gilead Sciences [14]. Despite unrestricted access to free DAA, only 30% of Georgian patients included in this study had started treatment.

Our study also documented large intra-regional variations in uptake of DAAs. Even though restrictions on reimbursement for DAAs have been removed gradually in many European countries during the study period [8], treatment uptake remained modest, even within countries with no reimbursement restrictions, although the numbers should be interpreted cautiously due few individuals under follow up in some countries. The World Health Organization has set a goal of eliminating HCV infection as a public health care threat by 2030 and recommends that all HIV/HCV co-infected persons are given effective treatment for both infections as a priority [19]. Our data indicates that by 2016 only few European countries are on track to achieve this goal.

The incidence in uptake of DAA-based therapy continued to increase from 2015 to 2016 in all regions except South where it decreased by 46%. The reason for this sharp drop is unclear, but could be due to a "warehousing effect" where the high incidence in 2014 and 2015 was driven by large groups of patients who had waited for the introduction of effective therapy leaving fewer eligible for therapy in the remaining cohort.

In 2015/2016 9% of all treatment regimens were IFN+RBV. The uptake of IFN+RBV was restricted to 16 countries from all regions of EuroSIDA, and used for all genotypes. IFN+RBV were until recently the recommended regimen for treatment of acute HCV infection [7]. Only nine out of 66 patients starting IFN+RBV in 2015/2016 had their first positive HCV-RNA in the 12 months before starting treatment. Thus treatment of acute infection only plays a minor role in the continued use of IFN+RBV.

Although persons with cirrhosis were more likely to be prioritized for DAA treatment compared with persons with lower stages of fibrosis, 11% of untreated persons had signs of cirrhosis, and hence are at increased short-term risk of liver-related complications if they do not get access to effective HCV treatment. Reasons for not starting therapy are not collected in EuroSIDA, but in addition to non-availability of anti-HCV drugs, comorbidities, ongoing illicit drug or alcohol abuse and other causes of unstable life circumstances perceived to be associated with non-adherence to therapy are likely reasons for not starting therapy.

Women were also less likely to receive DAA therapy than men, even after adjustment for other factors associated with starting therapy. Large trials have found no differences in effectiveness and safety of DAAs according to gender [20, 21]. An earlier EuroSIDA study on the uptake of HCV treatment in the IFN era, found no differences according to gender [22]. The gender difference was most pronounced among those younger than 35 years of age, and was consistent across regions and in all sensitivity analyses. There were no gender differences in use of cART or proportion with suppressed HIV-RNA, but women had slightly longer times between CD4 and HIV-RNA measurements which might suggest less frequent clinic visit. DAAs are generally contraindicated during pregnancy and breastfeeding [23], but given the short duration of DAA therapy and the age distribution of the cohort, the effect of pregnancy on DAA uptake seems minimal. Residual confounding cannot be excluded.

An important, but not unexpected finding was that lack of engagement in HIV care (defined as not receiving cART or having unsuppressed HIV-RNA) was associated with lower incidence of starting DAA. Hence barriers in the HIV care continuum are linked to poorer outcomes in HCV care, and should be addressed in a concerted manner to improve outcomes for both infections. There was a trend towards a lower incidence of DAA uptake among persons with a history of

IDU, although it did not reach statistical significance. Studies have confirmed that DAAs are effective among IDUs and guidelines recommend that all HCV infected persons, including IDUs, should be considered for therapy [7, 24].

Study limitations

This study has some limitations that should be mentioned.

Although EuroSIDA seeks to include a representative sample of participants from all European countries, participants are mainly recruited from university clinics in large European cities and not in exact proportion to the infected population in each country, and may therefore not be representative of the entire HIV/HCV co-infected population in Europe. Among all anti-HCV positive individuals followed up after 2011, 1273 (17.9%) have unknown HCV-RNA status (not tested or not reported). Both factors might have led us to overestimate the incidence of HCV treatment, particularly in East where 710/1670 (42.5%) of all anti-HCV positive persons had unknown HCV-RNA. In the majority of participants, staging of liver fibrosis was based on APRI. Compared with liver biopsy, APRI is known to misclassify the fibrosis stage in some individuals, particularly in those with intermediate stage of fibrosis [25]. Furthermore, we not able to analyze the role of missed visits and/or frequency of visits for HIV care. The major strengths of this study is that it prospectively follows a large population of co-infected persons in a heterogeneous real-life setting across all regions of Europe, and that we have longitudinal data collected in a standardised way to allow temporal changes to be described.

CONCLUSIONS

Although the use of effective and well-tolerated DAAs against HCV have increased markedly among HIV/HCV co-infected patients in Europe in general since 2014, cost of the drugs and

other barriers to treatment prevent them from reaching some of the patients most at need of HCV treatment. Further follow up to monitor access to DAA therapy to achieve the WHO HCV elimination goal in 2030 among HIV/HCV co-infected in Europe is warranted.

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Figure legends

Figure 1: The figure shows the proportion of different HCV treatment regimens (PEG-IFN + ribavirin, PEG-IFN + DAA, IFN-free DAA) started during prospective follow up and stratified by EuroSIDA region

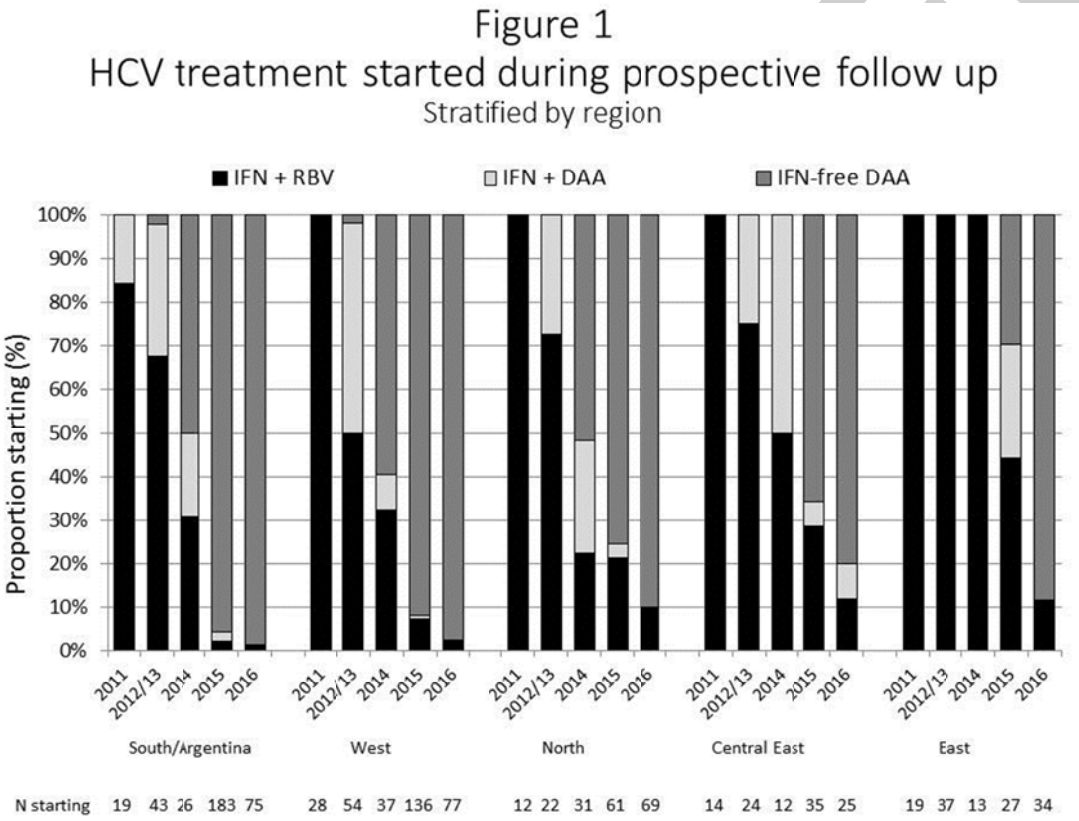
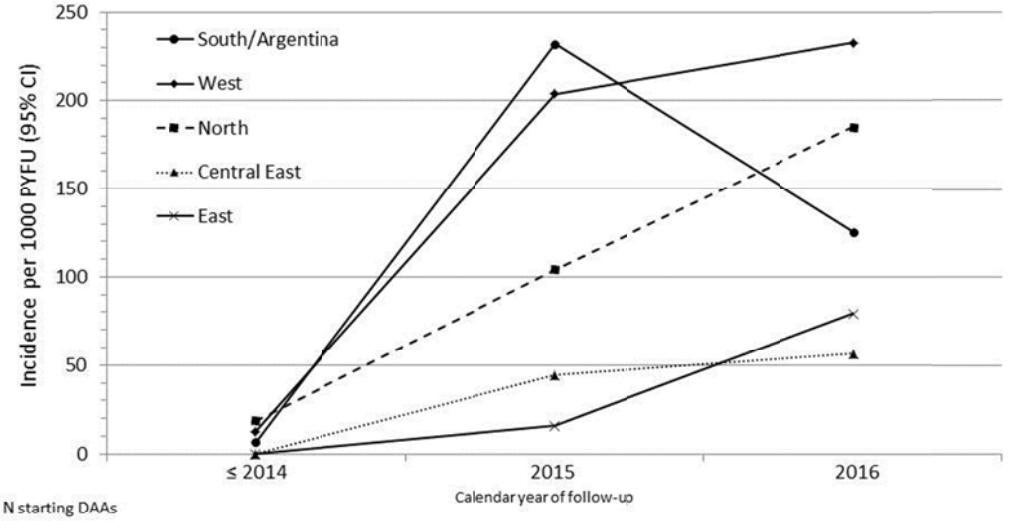


Figure 2: The figure shows the incidence of starting IFN-free DAA therapy during prospective follow up and stratified by EuroSIDA region



N starting DAAs			
South/Argentina	14	193	75
West	29	122	75
North	20	47	63
Central East	0	24	24
East	0	8	31

Figure 3

The figure shows the uptake of IFN-free DAA therapy in 34 individual EuroSIDA countries according to region of Europe and number of HIV/HCV co-infected under follow up in 2016. The bubble size and the annotation above each bubble represent the number of individuals in each country

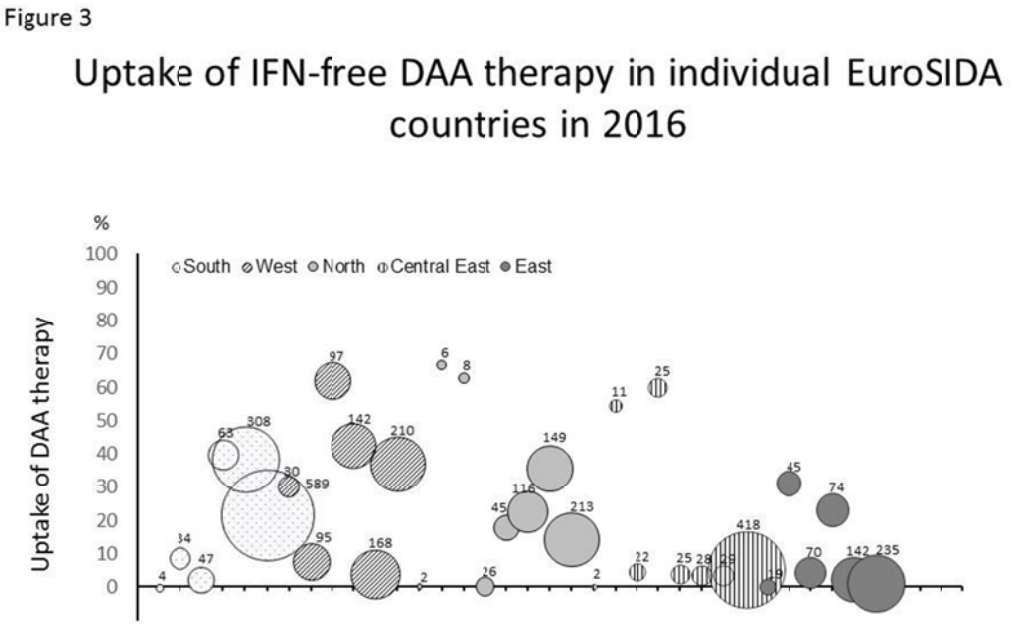
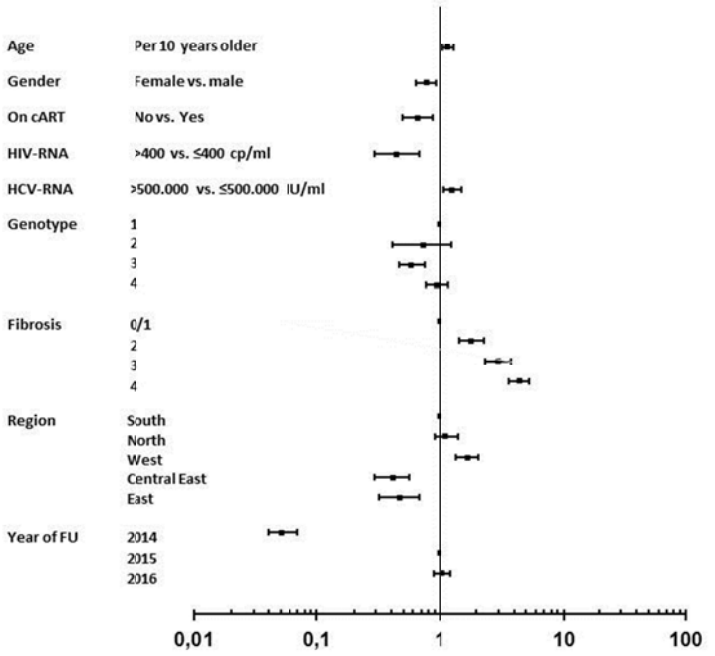


Figure 4: The figure shows the adjusted incidence rate ratios of starting IFN-free DAA therapy during follow up.

The model is adjusted for the factors shown plus HIV transmission group, CD4 cell count, nadir CD4, prior AIDS, HBsAg, and HCV treatment at baseline

Figure 4
Adjusted incidence rate ratios of starting IFN-free DAA during follow up



Abbreviations: IDU: injection drug use; cART: combination antiretroviral therapy; FU: follow up; HBsAg: hepatitis B surface antigen

Table 1. Characteristics at time of starting HCV treatment or at last follow up in untreated

		Total		Untreated		Started treatment		P
All		4308	100.0	3195	74.2	1113	25.8	
Gender	Male	3110	72.2	2250	70.4	860	77.3	<0.0001
	Female	1198	27.8	945	29.6	253	22.7	
Race	White	3842	89.2	2882	90.2	960	86.3	0.0003
	Other	466	10.8	313	9.8	153	13.7	
Region	South/Argentina	1255	29.1	909	28.5	346	31.1	<0.0001
	West	970	22.5	638	20.0	332	29.8	
	North	663	15.4	468	14.6	195	17.5	
	Central East	633	14.7	523	16.4	110	9.9	
	East	788	18.3	657	20.6	130	11.7	
HIV risk	MSM	808	18.8	546	17.1	262	23.5	<0.0001
	IDU	2531	58.8	1930	60.4	601	54.0	
	Hetero	636	14.8	486	15.2	150	13.5	
	Other/unknown	333	7.7	233	7.3	100	9.0	
HCV-RNA (IU/ml)	≤500.000	1586	36.8	1234	38.6	352	31.6	<0.0001
	>500.000	2579	59.9	1830	57.3	749	67.3	
	Unknown	143	3.3	131	4.1	12	1.1	
Genotype	Unknown	1223	28.4	931	29.1	292	26.2	0.026
	1	1721	39.9	1234	38.6	487	43.8	
	2	81	1.9	62	1.9	19	1.7	
	3	799	18.5	613	19.2	186	16.7	
	4	484	11.2	355	11.1	129	11.6	
Fibrosis Stage	0/1	2837	65.9	2273	71.1	564	50.7	<0.0001
	2	482	11.2	331	10.4	151	13.6	
	3	303	7.0	172	5.4	131	11.8	
	4	585	13.6	339	10.6	246	22.1	
	Unknown	101	2.3	80	2.5	21	1.9	
	Yes	1370	31.8	994	31.1	376	33.8	0.099
HCV Tx at baseline	IFN/RBV	1206	28.0	863	27.0	343	30.8	0.015
	IFN/RBV/DAA	100	2.3	74	2.3	26	2.3	0.97
	DAA only	107	2.5	99	3.1	8	0.7	<0.0001
HBsAg	Negative	3714	86.2	2759	86.4	955	85.8	0.17
	Positive	184	4.3	144	4.5	40	3.6	
	Unknown	410	9.5	292	9.1	118	10.6	
Ever cART	No	305	7.1	213	6.7	92	8.3	0.073
	Yes	4003	92.9	2982	92.3	1021	91.7	
HIV-	No	444	10.4	366	11.5	78	7.1	<0.0001

RNA <500	Yes	3820	89.6	2803	88.5	1017	92.9	
		Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**P**
Age	Years	45	38 – 51	45	37 – 50	47	40 - 52	<0.0001
CD4	/mm^3	552	374 – 772	548	364 – 773	570	401 - 770	0.0070
Last visit	Mm/yy	06/16	6/15 – 10/16	8/16	2/16 – 10/16	5/15	01/14 – 01/16	<0.0001

Abbreviations: MSM: men who have sex with men; IDU: injection drug use; IFN: interferon; RBV: ribavirin; DAA: direct-acting antiviral; HBsAg: hepatitis B surface antigen; cART: combination antiretroviral therapy; IQR: interquartile range