HCV reinfection after HCV therapy among HIV/HCV co-infected individuals in Europe

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Abstract

Background

While direct acting antivirals (DAA) can clear HCV in nearly all HIV/HCV coinfected individuals, high rates of reinfection may hamper efforts to eliminate HCV in this population. We investigated reinfection after sustained virologic response (SVR) in HIV/HCV coinfected individuals in Europe.

Methods

Factors associated with odds of reinfection by two years after SVR in EuroSIDA participants with ≥1 HCV-RNA test and 2 years follow-up were assessed using logistic regression.

Results

Overall, 1,022 individuals were included. The median age was 50 (IQR 43-54 years), and most were male (78%), injection drug users (52%), and received interferon (IFN)-free DAA (62%). By 24 months, 75 (7.3%, 95% confidence interval [CI] 5.7%-8.9%) individuals were reinfected. Among individuals treated prior to 2014, 16.1% were reinfected compared with 4.2% and 8.3% among those treated ≥2014 with IFN-free and IFN-based therapy, respectively. After adjustment, individuals who had started treatment ≥2014 with IFN-free or IFN-based therapy had significantly lower odds of reinfection (adjusted odds ratio 0.21, 95% CI: 0.11-0.38 and 0.43, 95% CI: 0.22-0.83) compared with those who had received therapy <2014. There were no significant differences in odds of reinfection according to age, gender, European region, HIV transmission risk group or liver fibrosis.

Conclusions

Among HIV/HCV coinfected individuals in Europe, 7.3% were HCV reinfected within 24 months of achieving SVR, with evidence suggesting this is decreasing over time and with use of newer HCV regimens. Harm reduction to reduce reinfection and surveillance to detect early reinfection with an offer of treatment is essential to eliminate HCV.

Introduction

While treatment with direct-acting antivirals (DAA) can cure hepatitis C virus infection in more than 95% of those treated [1], high rates of HCV reinfection could hamper efforts to achieve the WHO goals of eliminating HCV infection as public health risk by 2030 [2].

In the era of interferon (IFN)-based HCV therapy, high risk of HCV reinfection has been described among HIV/HCV coinfected individuals. A meta-analysis found that HIV/HCV coinfected individuals had a 15% risk of reinfection after achieving sustained virological response (SVR) with pegylated interferon and ribavirin, with those treated outside randomzied clinical trials being at particular high risk of reinfection [3].

In the era of DAA therapy, real-life studies of HCV reinfection among HIV positive persons have primarily come from cohorts in Western Europe [4, 5], Australia [6] and Canada [7]. In Europe, high rates of HCV reinfection have been observed among HIV positive MSM in studies from Spain[5] with 5.93 reinfections per 100 person-years of follow up (95% confidence interval 3.37-10.44) and Germany [4] 9.02 (6.48-12.26). In the same studies the reinfection rates among injecting drug users (IDUs) were only 0.21 (0.09-0.52) and 1.14 (0.56–2.09), respectively. There is a lack of data on HCV reinfection from more heterogeneous European HIV positive populations including patients followed in clinics in Eastern Europe.

In this analysis we aimed to evaluate the two-year prevalence of HCV reinfection after IFN-based or IFN-free DAA HCV therapy among HIV/HCV coinfected individuals from the pan-European EuroSIDA cohort study.

Methods

Study design and participants

Pariticipants were recruited from the EuroSIDA study, a large prospective observational cohort study of HIV-infected individuals, that has enrolled around 23,000 HIV-1 infected individuals from around 100 clinics across 35 countries across all regions of Europe as well as Israel and Argentina.

The EuroSIDA study has been described in detail elsewhere [8]. Standardised data including information on demographics, HIV-related factors, antiretroviral therapy (ART), coinfections, comorbidities and routine biochemistry are collected at enrolment and, thereafter, once annually. Detailed information is collected on HCV serology, virology, liver fibrosis and HCV treatment including individual drugs and start and stop dates of treatment [9].

Eligible for this analysis were those who had achieved an SVR after IFN-based or IFN-free HCV therapy during prospective follow-up, and had at least 24 months of follow up after SVR and at least one HCV-RNA result during that period. Where individuals had more than one treatment episode during follow-up, the first episode with SVR was used.

Outcomes and definitions

The primary outcome of interest was HCV reinfection during the 24-month follow up period following SVR. SVR was defined as undetectable HCV-RNA 12 weeks or 24 weeks after HCV treatment course completion for IFN-free and IFN-based therapy, respectively. HCV reinfection was defined as any positive HCV-RNA or genotype result or initiation of HCV therapy within this 24-month follow up period. Baseline was defined as the date of SVR.

Liver fibrosis was defined according to the definitions previously used in the EuroSIDA study based on liver biopsy and Fibroscan® test results, aspartate transaminase to platelet ratio (APRI), or plasma hyaluronic acid. Fibrosis stage was defined based on the most recent fibrosis marker measured before the baseline. Advanced fibrosis (METAVIR ≥F3) was defined as either ≥F3 on liver biopsi, Fibroscan ≥9 kPa, APRI>1.5 or hyaluronic acid >160 ng/mL. Where >1 marker was measured priority was given to biopsy, Fibroscan, APRI followed by hyaluronic acid [10].

Statistical methods

Characteristics of included participants at baseline were described and compared between those with or without reinfection during follow up, using chi-squared tests for categorical variables and Kruskall-Wallis tests for continuous variables.

Logistic regression was used to determine the odds of being HCV reinfected. Variables that were significant in univariable analysis ($p<0.1$) were adjusted for in the multivariable model and including year of treatment/HCV regimen (categorised as <2014; ≥2014/IFN-free DAA; ≥2014/IFN +/- DAA) and region of Europe *a priori*. Analyses were performed using SAS (Statistical Analysis Software, version 9.4, Cary NC, US)

Results

Among 23,005 HIV-1 infected persons in EuroSIDA, 9,276 were HCV-Ab positive and 6,915 (74.5%) were ever HCV-RNA positive. Among these, 2,625 (38.0%) had achieved SVR after EuroSIDA enrolment and 1,579 (60.2%) had at least 24 months of follow up after SVR and among these, 1,022 (64.7%) had been tested for HCV-

RNA at least once within 24 months of achieving SVR and were included in this study. Compared with those included, excluded individuals were younger, less likely to be male, to have a later baseline, and more likely to be from Central East or Eastern Europe and less likely to be from Central or Northern Europe compared to Southern Europe. Excluded partcipipants were also more likely to have ≤F3 liver fibrosis. There were no differences between the groups in terms of HIV related factors.

Among the 1,022 included individuals, the majority were male (78%), white (86%), with a median age of 50 years (interquartile range [IQR]: 43-54) and 52% reported IDU as the mode of HIV infection; 146 (14%) were enrolled from the East/Central-East regions. The median (IQR) CD4 cell count was 596 (426-818) cells/mm^3 and 96% were on ART. Nineteen percent of the individuals achieved SVR before 2014, when treatment was largely interferon-based (91%), and 60% achieved SVR at/after 2014 with an interferon-free DAA-based regimen. Thirty percent had advanced liver fibrosis (METAVIR stage F3-F4).

During two years of follow up, 75 (7.3%, 95% confidence interval [CI] 5.7%-8.9%) individuals were reinfected. Table 1 compares the characteristics of the three groups categorized according to treatment year and HCV treatment regimen (individuals treated <2014; treatment ≥2014/IFN-free DAA; treatment ≥2014/IFN +/- DAA). The reinfection rate was highest among those treated before 2014 (16.1%) vs. ≥2014 with IFN-free DAAs (4.2%) or with IFN +/- DAA (8.3%; p<0.0001). The characteristics of the three goups differed significantly except for gender. Of note, among those treated prior to 2014, 58% had IDU as HIV transmission risk, while 22% were MSM. Among those treated >2014, the proportion of IDU decreased significantly, while the proportion of MSM increased, compared with individuals treated prior to 2014.

Those with a baseline of ≥2014 and treated with DAA had the highest median number of HCV-RNA measurements during the 2 year FU (3 tests, IQR 2–3) compared to those treated before 2014 (2 tests, IQR 2-3) or those treated with IFN ≥2014 (2 tests, IQR 2-3, p=0.0020). The median (IQR) number of HCV-RNA tests during the 2 year FU period following SVR was highest (4 tests, IQR 2-7) in those reinfected than among those not reinfected (2 tests, IQR 2-3; p<0.0001). The median time to reinfection was 8 months (IQR 2 – 19) overall, and was similar across the three treatment groups (p=0.57; baseline <2014, baseline ≥2014 treated with IFN and baseline ≥2014 treated with DAAs).

Figure 1 shows factors associated with odds of reinfection. In multivariable analysis individuals who had started treatment ≥2014 with IFN-free DAA therapy or IFN-based therapy (+/- DAA) had significantly lower odds of reinfection (adjusted odds ratio [aOR] 0.21, 95% CI: 0.11-0.38 and aOR 0.43, 95% CI 0.22-0.83) compared with those who had received therapy prior to 2014. No other factors were significantly associated with reinfection after adjustment. Of note, there were no significant differences in odds of reinfection when comparing injection drug users vs. MSM, or when comparing those with METAVIR F3/F4 fibrosis vs. <F3 fibrosis at baseline.

Discussion

In this analyses that included 1,022 HIV/HCV coinfected individuals from all regions of Europe who had achieved SVR after IFN-based or IFN-free therapy, 75 (7.3%) were HCV reinfected within two years of achieving SVR.

Although those achieving SVR in 2014 or later had an almost four-fold lower odds of reinfection compared with those achieving SVR prior to 2014, we found no differences in odds of reinfection when comparing IFN-treated (+/- DAA) in 2014 or later with those who had received IFN-free DAA therapy in the same period. Hence our data do not indicate that the ease of short, well-tolerated and effective DAA therapy compared with IFN-based therapy leads to increased risk disinhibition and high rates of HCV reinfection after DAA therapy in this population. Lower odds of reinfection among those treated in recent years can possibly be explained by a lower prevalence of HCV infection in the population due to the scale up of DAA since 2014. This is supported by an Australian study showing a low risk of reinfection following unrestricted access to DAA despite ongoing risk behaviour [6], and studies from Europe that have found a decrease in the incidence of primary HCV infection among HIV infected individuals after universal access to DAA [11, 12].

Our study is one of the first to report data from Eastern Europe and Central East, regions with a high prevalence of HIV/HCV coinfected injection drug users and low access to needle- and syringe exchange programmes and opioid substitution therapy [13]. However, there was no evidence that individuals from Central East/East Europe had increased odds of reinfection, but this was based on relatively few individuals and more studies from Eastern Europe are therefore still needed.

Although reinfection was more common among MSM than among with those with IDU as main HIV transmission risk, the difference was not statistically significant after adjusting for other risk factors. This is in contrast to studies from Germany [4] and

Spain [5], that found much higher reinfection rates among DAA treated MSM than in IDU. Unfortunately, in EuroSIDA we do not know if the IDU are currently injecting. In Spain and Germany drug users have access to comprehensive preventive measures against blood borne infections, whereas coverage varies across other European countries [13] and a direct comparison with the IDU population from our study is not possible.

Although all individuals considered for inclusion in this study were under active follow up for their HIV infection, around a third had no documented HCV-RNA result in the first two years after SVR and were therefore not included in the study. Lack of HCV-RNA testing after SVRmeans many reinfections may go unnoticed with risk of fibrosis progression for the individuals and onward tranmission to others. We also found that individuals who were reinfected had a higher median HCV-RNA tests during the 2 year follow up period than those who were not reinfected (4 vs. 2 tests). It is possible that individuals considered to have symptoms and/or ongoing risk-behaviour were preferentially targeted for HCV-RNA testing and that the study therefore overestimates the rate of reinfection.

The strengths of this study is the inclusion of a large diverse population from across Europe and that all persons were followed for at least 2 years to observe reinfection. In addition to missing HCV-RNA testing after SVR described above, other limitations include lack of information about ongoing transmission risk behaviour and access to preventive measures such as needle-exchange programs and opiod substitution therapy. Since viral sequenzing is not collected in EuroSIDA, we were unable to definitively differentiate reinfections from late relapses. However, since relapses later than 12 and 24 weeks after end of INF-free and IFN-based therapy are relatively uncommon [14, 15], this limitation is not likely to influence the conclusions of our study significantly.

In conclusion, this study of 1,022 HIV/HCV coinfected persons from all regions of Europe, found that the HCV reinfection rate in the first two years after SVR was 7.3%, but with lower odds of reinfection among those treated in recent years or using IFN-free DAA therapy. More studies of HCV reinfection among HIV co-infected individuals, followed up for longer time are warranted.

Author Contribution Statement

SA, AKS, AMO and LP conceived the study, designed the analyses and interpreted the findings. SA, AKS and AMO performed the statistical analyses. SA and AKS wrote the first manuscript draft. AM and LP reviewed and commented on the first and subsequent drafts. AR, LV, TB, AMI, CD, HST, HSA, NC, LC, ML, PD, GW, MG, EK, GD, BK, RM and JKR contributed data to the study. AR, LV, TB, AMI, CD, HST, HSA, NC, LC, ML, PD, GW, MG, EK, GD, BK, RM, JKR and JDL reviewed and commented on the final draft of the manuscript and were involved in the interpretation of findings.

Conflicts of interest

Thomas Benfield reports grants from Novo Nordisk Foundation, grants from Simonsen Foundation, grants and personal fees from GSK, grants and personal fees from Pfizer, personal fees from Boehringer Ingelheim, grants and personal fees from Gilead, personal fees from MSD, grants from Lundbeck Foundation, grants from Kai Hansen Foundation, personal fees from Pentabase ApS, grants from Erik and Susanna Olesen's Charitable Fund, outside the submitted work.

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All other authors report no conclicts of interest

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FIGURE LEGEND

The figure shows the odds the adjusted odds ratio of HCV reinfection within 24 months of achiveving sustained virological response with either direct-acting antivirals or interferon-based therapy.

Abbreviations: DAA, direct-acting antivirals; IFN, interferon; MSM, men who have sex with men; IDU, injecting drug use;

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