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HCV reinfection after HCV therapy among HIV/HCV-coinfected individuals in Europe / Amele, S., Sandri, A.K., Rodger, A., Vandekerckhove, L., Benfield, T., Milinkovic, A., Duvivier, C., Stellbrink, H.-J., Sambatakou, H., Chkhartishvili, N., Caldeira, L., Laguno, M., Domingo, P., Wandeler, G., Gisinger, M., Kuzovatova, E., Dragovic, G., Knysz, B., Matulionyte, R., Rockstroh, J.K., et al.. - In: HIV MEDICINE. - ISSN 1464-2662. - 23:6(2022), pp. 684-692. [10.1111/hiv.13212]

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20/06/2026 16:08

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

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Word count abstract: 250

Word count for main body of manuscript: 1908

Tables and Figures: One table and one figure

1 **Abstract**

2 **Background**

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

7

8 **Methods**

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

12

13 **Results**

14 Overall, 1,022 individuals were included. The median age was 50 (IQR 43-54 years),
15 and most were male (78%), injection drug users (52%), and received interferon
16 (IFN)-free DAA (62%). By 24 months, 75 (7.3%, 95% confidence interval [CI] 5.7%-
17 8.9%) individuals were reinfected. Among individuals treated prior to 2014, 16.1%
18 were reinfected compared with 4.2% and 8.3% among those treated ≥ 2014 with
19 IFN-free and IFN-based therapy, respectively. After adjustment, individuals who had
20 started treatment ≥ 2014 with IFN-free or IFN-based therapy had significantly lower
21 odds of reinfection (adjusted odds ratio 0.21, 95% CI: 0.11-0.38 and 0.43, 95% CI:
22 0.22-0.83) compared with those who had received therapy < 2014 . There were no
23 significant differences in odds of reinfection according to age, gender, European
24 region, HIV transmission risk group or liver fibrosis.

25

26 **Conclusions**

27 Among HIV/HCV coinfecting individuals in Europe, 7.3% were HCV reinfected within
28 24 months of achieving SVR, with evidence suggesting this is decreasing over time
29 and with use of newer HCV regimens. Harm reduction to reduce reinfection and
30 surveillance to detect early reinfection with an offer of treatment is essential to
31 eliminate HCV.

32 **Introduction**

33 While treatment with direct-acting antivirals (DAA) can cure hepatitis C virus infection
34 in more than 95% of those treated [1], high rates of HCV reinfection could hamper
35 efforts to achieve the WHO goals of eliminating HCV infection as public health risk by
36 2030 [2].

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

43 In the era of DAA therapy, real-life studies of HCV reinfection among HIV positive
44 persons have primarily come from cohorts in Western Europe [4, 5], Australia [6]
45 and Canada [7]. In Europe, high rates of HCV reinfection have been observed among
46 HIV positive MSM in studies from Spain[5] with 5.93 reinfections per 100 person-
47 years of follow up (95% confidence interval 3.37-10.44) and Germany [4] 9.02
48 (6.48-12.26). In the same studies the reinfection rates among injecting drug users
49 (IDUs) were only 0.21 (0.09-0.52) and 1.14 (0.56-2.09), respectively. There is a
50 lack of data on HCV reinfection from more heterogeneous European HIV positive
51 populations including patients followed in clinics in Eastern Europe.

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

55

56 **Methods**

57 *Study design and participants*

58 Participants were recruited from the EuroSIDA study, a large prospective
59 observational cohort study of HIV-infected individuals, that has enrolled around
60 23,000 HIV-1 infected individuals from around 100 clinics across 35 countries across
61 all regions of Europe as well as Israel and Argentina.

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

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

73

74 *Outcomes and definitions*

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

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

88

89 *Statistical methods*

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

93 Logistic regression was used to determine the odds of being HCV reinfected. Variables
94 that were significant in univariable analysis ($p < 0.1$) were adjusted for in the
95 multivariable model and including year of treatment/HCV regimen (categorised as
96 $<$ 2014; \geq 2014/IFN-free DAA; \geq 2014/IFN +/- DAA) and region of Europe *a priori*.
97 Analyses were performed using SAS (Statistical Analysis Software, version 9.4, Cary
98 NC, US)

99

100 **Results**

101 Among 23,005 HIV-1 infected persons in EuroSIDA, 9,276 were HCV-Ab positive and
102 6,915 (74.5%) were ever HCV-RNA positive. Among these, 2,625 (38.0%) had
103 achieved SVR after EuroSIDA enrolment and 1,579 (60.2%) had at least 24 months
104 of follow up after SVR and among these, 1,022 (64.7%) had been tested for HCV-

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

111

112 Among the 1,022 included individuals, the majority were male (78%), white (86%),
113 with a median age of 50 years (interquartile range [IQR]: 43-54) and 52% reported
114 IDU as the mode of HIV infection; 146 (14%) were enrolled from the East/Central-
115 East regions. The median (IQR) CD4 cell count was 596 (426-818) cells/mm³ and
116 96% were on ART. Nineteen percent of the individuals achieved SVR before 2014,
117 when treatment was largely interferon-based (91%), and 60% achieved SVR at/after
118 2014 with an interferon-free DAA-based regimen. Thirty percent had advanced liver
119 fibrosis (METAVIR stage F3-F4).

120

121 During two years of follow up, 75 (7.3%, 95% confidence interval [CI] 5.7%-8.9%)
122 individuals were reinfected. Table 1 compares the characteristics of the three groups
123 categorized according to treatment year and HCV treatment regimen (individuals
124 treated <2014; treatment \geq 2014/IFN-free DAA; treatment \geq 2014/IFN +/- DAA).
125 The reinfection rate was highest among those treated before 2014 (16.1%) vs.
126 \geq 2014 with IFN-free DAAs (4.2%) or with IFN +/- DAA (8.3%; $p < 0.0001$). The
127 characteristics of the three groups differed significantly except for gender. Of note,
128 among those treated prior to 2014, 58% had IDU as HIV transmission risk, while
129 22% were MSM. Among those treated >2014, the proportion of IDU decreased
130 significantly, while the proportion of MSM increased, compared with individuals
131 treated prior to 2014.

132 Those with a baseline of \geq 2014 and treated with DAA had the highest median number
133 of HCV-RNA measurements during the 2 year FU (3 tests, IQR 2-3) compared to
134 those treated before 2014 (2 tests, IQR 2-3) or those treated with IFN \geq 2014 (2
135 tests, IQR 2-3, $p = 0.0020$). The median (IQR) number of HCV-RNA tests during the
136 2 year FU period following SVR was highest (4 tests, IQR 2-7) in those reinfected
137 than among those not reinfected (2 tests, IQR 2-3; $p < 0.0001$). The median time to
138 reinfection was 8 months (IQR 2 - 19) overall, and was similar across the three
139 treatment groups ($p = 0.57$; baseline <2014, baseline \geq 2014 treated with IFN and
140 baseline \geq 2014 treated with DAAs).

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

149

150 **Discussion**

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

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

167

168 Our study is one of the first to report data from Eastern Europe and Central East,
169 regions with a high prevalence of HIV/HCV coinfecting injection drug users and low
170 access to needle- and syringe exchange programmes and opioid substitution therapy
171 [13]. However, there was no evidence that individuals from Central East/East Europe
172 had increased odds of reinfection, but this was based on relatively few individuals
173 and more studies from Eastern Europe are therefore still needed.

174

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

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

184

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

195

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

206

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

212

213 **Author Contribution Statement**

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

221

222

223 **Conflicts of interest**

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

230 Jürgen Rockstroh reports honoraria, consultancy fees, travel support and/or lecture
231 fees from Abivax, Galapagos, Gilead, Janssen, Merck, Theratechnologies, and ViiV,
232 outside the submitted work

233 Raimonda Matulionyte reports educational grants, consultancy fees, travel support
234 and/or lecture fees from Abbvie, Johnson and Johnson, MSD, ViiV Healthcare,
235 GlaxoSmithKline, INTEGRATE and WEEPI project grants, outside the submitted
236 work.

237 Amanda Mcroft reports honoraria, consultancy fees, travel support and/or lecture
238 fees from Gilead, ViiV and Eiland and Bonnin PC, outside the submitted work

239 All other authors report no conflicts of interest

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 DNR126] from the Danish National Research Foundation and by the International Cohort Consortium of Infectious Disease (RESPOND).

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FIGURE LEGEND

The figure shows the odds the adjusted odds ratio of HCV reinfection within 24 months of achieving 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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