Drug plasma trough concentrations during treatment with daclatasvir and sofosbuvir are associated respectively with liver impairment and with renal dysfunction in HIV/HCV co-infected patients.

Ilaria Mastrorosa¹†, Massimo Tempestilli²†*, Stefania Notari², Patrizia Lorenzini¹, Gabriele Fabbri¹, Federico Lupi¹, Rita Bellagamba¹, Alessandra Vergori¹, Mauro Zaccarelli¹, Chiara. Agrati², Andrea Antinori¹, Adriana Ammasari¹

¹ Clinical Department, National Institute for Infectious Diseases “L. Spallanzani” I.R.C.C.S., Via Portuense 292, 00149, Rome, Italy
² Cellular Immunology and Pharmacology Laboratory, National Institute for Infectious Diseases “L. Spallanzani” I.R.C.C.S., Via Portuense 292, 00149, Rome, Italy

† These authors contributed equally to the manuscript

*Corresponding Author:
Massimo Tempestilli, Cellular Immunology and Pharmacology Laboratory, National Institute for Infectious Diseases “L. Spallanzani” I.R.C.C.S., Via Portuense 292, 00149, Rome, Italy.
Phone: +39 0655170972, e-mail: massimo.tempestilli@inmi.it

Email addresses of co-authors:
Ilaria Mastrorosa(ilariamastrorosa@gmail.com); Stefania Notari (stefania.notari@inmi.it); Patrizia Lorenzini (patrizia.lorenzini@inmi.it), Gabriele Fabbri (gabriele.fabbri@inmi.it); Federico Lupi (federico.lupi@inmi.it); Rita Bellagamba (rita.bellagamba@inmi.it); Alessandra Vergori (alessandra.vergori@inmi.it); Mauro Zaccarelli
Abstract

Background: Sofosbuvir (SOF) plus daclatasvir (DCV) achieved high rates of sustained virologic response (SVR) with no difference according to HIV serostatus. Only limited information is available on the pharmacokinetics variability of SOF and DCV in HIV/HCV co-infected patients. Aim was to evaluate the association of plasma drug concentrations (C_{trough}) of SOF and of DCV with patient-, treatment-, and disease-related factors in the real-world setting of HIV/HCV co-infected persons.

Methods: In this observational cohort study, HIV/HCV co-infected patients, undergoing SOF plus DCV treatment, were prospectively enrolled. At baseline, week4 (W4), end of treatment (EOT), and after-EOT, biochemical and viro-immunological parameters were assessed. FIB-4 score and CKD-EPI equation were used for estimation of liver disease and glomerular filtration rate (eGFR), respectively. SOF, SOF metabolite (GS-331007), and DCV C_{trough} were measured at W4 and week8 (W8), and the mean value (mean-C_{trough}) was calculated.

Results: Thirty-five patients were included (SVR 94%). Increasing GS-331007 mean-C_{trough} significantly correlated with decreasing eGFR at W4 (rho=-0.36; p=0.037) and EOT (rho=-0.34; p=0.048). Between DCV mean-C_{trough} and FIB-4,
a significant correlation was observed at all time-points: baseline (rho=-0.35; p=0.037), W4 (rho=-0.44; p=0.008), EOT (rho=-0.40; p=0.023), after-EOT (rho=-0.39; p=0.028).

**Conclusion:** In HIV/HCV co-infected patients receiving SOF plus DCV, plasma drug concentrations are associated with renal dysfunction for GS-331007 and with liver impairment for DCV. Though clinical and therapeutically relevance of these findings may apparently be limited, growth of clinicians' knowledge on DAA exposure in difficult-to-treat patients, as cirrhotic and renal impaired subjects, can be relevant in single cases.

**Keywords:** Direct-Acting Antivirals; HIV/HCV; Kidney; Liver; Pharmacokinetic

**Background**

The development of peginterferon-free (pegIFN-free) oral regimens of direct-acting antivirals (DAA) greatly improved the efficacy and tolerability of HCV treatment in HIV co-infected population [1-3]. Achieving sustained virological response (SVR) after treatment is associated to regression of hepatic disease, including fibrosis reduction, as well as to improvement of several comorbid conditions [4-5].

The combination of a nucleotide-analogous inhibitor of HCV NS5B polymerase, as sofosbuvir (SOF), plus an inhibitor of HCV NS5A replication complex, as daclatasvir (DCV), ledipasvir or velpatasvir, with or without ribavirin, are treatment options for HCV therapy [6-7].

Focusing on the pan-genotypic DAA combination SOF plus DCV, they are both dosed once daily and have favorable safety profiles [8-9]. In phase III randomized
clinical trials, this regimen achieved high SVR rates without difference by HIV sero-status, but with worse outcomes in cirrhotic patients [3, 10, 11]. However, it is not clear if these SVR results may be replicated in the real-world HIV/HCV co-infection setting, where patients are expected to have more advanced liver disease and higher frequency of comorbidities, as renal disease as compared with clinical trials [12]. Indeed, liver and kidney dysfunction can affect drugs metabolism, including DAA that are cleared by liver, except SOF, which is mainly eliminated by kidney [13]. Only limited information is available on the pharmacokinetics of SOF and DCV in HIV/HCV co-infected patients and particularly on their variability based on liver and renal function. Thus, aim of the study was to evaluate the association of plasma drug concentrations ($C_{\text{trough}}$) of SOF and of DCV with patient-, treatment-, and disease-related factors in the real-world setting of HIV/HCV co-infected persons.

**Methods**

**Study design**

This study was a monocenter, prospective, observational study evaluating DAA $C_{\text{trough}}$ in HIV/HCV co-infected persons undergoing anti-HCV treatment with SOF and DCV at the National Institute for Infectious Diseases in Rome, Italy, between February 2015 and March 2016.

**Patients and HCV treatment**
Patients with HIV/HCV co-infection and treated with daily DCV (30 or 60 or 90 mg, based on drug to drug interactions with antiretrovirals) and SOF 400 mg together with antiretroviral therapy, were enrolled. 6-9 Physicians prescribed HCV treatment according to international treatment guidelines6,7 and criteria of the Italian Medicines Agency available during the study period (stage F3-F4 or any stage of fibrosis with HCV-associated extrahepatic manifestations). Biochemical and viro-immunological parameters were assessed at baseline, at week 4 (W4) during DAA treatment, at end of treatment (EOT), and after-EOT. SVR was defined by HCV RNA <12 copies/mL 12 weeks after-EOT (SVR12). Adherence to antiretrovirals and to DAA during the previous 4 weeks was self-reported through a visual analogue scale (VAS) ranging from 0 (no drug intake) to 100 (intake of all prescribed medications) and a Likert scale from 1 (no drug intake) up to 4 (intake of all prescribed medications).

Transient elastography before DAA start was used to measure stiffness and to classify fibrosis stage. The Fibrosis 4 score (FIB-4) for non-invasive liver disease assessment and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for glomerular filtration rate estimate (eGFR), were calculated using standard formulas at baseline, W4, EOT and after-EOT and used as marker of renal and hepatic function before, during and after DAA treatment.

**DAA plasma concentrations**

Venous blood samples for $C_{\text{trough}}$ levels were drawn at the end of dosing interval (20-24 hours post-dose) and assessed at W4 and W8 during DAA treatment. In order to decrease variability due to single $C_{\text{trough}}$ value, a mean value between the two time-points (mean-$C_{\text{trough}}$) was calculated.
As SOF becomes undetectable in blood 4–5 hours after administration due to intracellular activation to triphosphate GS-461203 (not detected in plasma) and ultimately to GS-331007, this latter is the predominant circulating metabolite and the primary analyte of interest in clinical pharmacology studies[8]. C_{trough} were determined for SOF, GS-331007, and DCV using a validated UPLC-MS/MS method. Limit of quantification were 11.71 ng/mL for SOF and DCV, and 19.53 ng/mL for GS-331007 [14].

**Statistical analysis**

Median and interquartile range (IQR) were used to summarize continuous variables and absolute frequencies with percentages for categorical variables. Statistical comparisons of SOF and DCV mean-C_{trough}, between different categories of factors, were made using Mann-Whitney test. To evaluate correlation between DAA mean-C_{trough} and continuous variables, Spearman rank correlation was calculated.

For the purpose of the study, we considered CKD-EPI at baseline as a marker of the pre-treatment renal function, and CKD-EPI at EOT and post-EOT to investigate renal function during and after DAA. FIB-4 at baseline and at W4 were used to evaluate hepatic function during the first month of DAA treatment [15]. Evaluated cut-offs were: 12 KPa for stiffness level, 3.25 at FIB-4 for severity of liver impairment, and 60 mL/min at CKD-EPI for impairment level of renal function. STATA 10.1 software was used for statistical analysis.

**Results**
**Patient population**

Thirty-five HIV/HCV co-infected patients were included and general characteristics were shown in Table 1 (first column). HCV-RNA at baseline was a median of 5.7 (IQR 5.1-6.1) log$_{10}$ copies/mL, and decreased by -4.6 [IQR -5.0-(-4.1)] copies/mL at W4 of DAA treatment. HCV-RNA at EOT was available in 32/35 patients because one patient died for non-liver-related cause, one was lost to follow-up, and blood test was not available for the third patient. Overall, SVR12 was achieved in 30/32 cases: 2 patients (6.2%), both cirrhotic with hepatocellular carcinoma, experienced virological failure.

Median FIB-4 decreased at the different time points and was 3.2 (IQR 2.1-5), 1.9 (IQR 1.6-3.9), 1.8 (IQR 1.4-3.3), 2.1 (IQR 1.5-3.3), at baseline, W4, EOT and after-EOT, respectively. Median values of CKD-EPI showed 96 mL/min (IQR 86-104) at baseline, 92 mL/min (IQR 83-103) at W4, 92 mL/min (IQR 82-99) at EOT, 95 mL/min (IQR 76-103) at after-EOT.

As shown in Table 1, no statistically significant associations were found between GS-331007 or DCV mean-C$_{\text{trough}}$ and most analyzed variables. Only renal (CKD-EPI) and liver function (FIB-4) significantly correlated with, respectively, GS-331007 and DCV C$_{\text{trough}}$ values.

**Sofosbuvir and renal function**

As expected, sofosbuvir was undetectable in all samples. The median GS-331007 C$_{\text{trough}}$ was 537 (IQR 324-738) ng/mL at W4 and 561 (IQR 380-800) ng/mL at W8, determining a median GS-331007 mean-C$_{\text{trough}}$ of 540 (IQR 358-797) ng/mL. In
the two subjects with treatment failure, median GS-331007 mean-C\textsubscript{trough} was 733 (IQR 674-793) ng/mL.

An inverse correlation was found between GS-331007 mean-C\textsubscript{trough} and eGFR: increasing plasma exposures were found with decreasing renal function at W4 (rho=-0.36; p=0.037) and at EOT (rho=-0.34; p=0.048). Notably, the association of GS-331007 mean-C\textsubscript{trough} with eGFR was not present at baseline (rho=-0.27; p=0.111) and was lost after-EOT (rho=0.021; p=0.906) (Fig. 1, panels a-b).

*Daclatasvir and liver impairment*

Median DCV C\textsubscript{trough} was 230 ng/mL (IQR, 140-368) and 254 ng/mL (IQR 154-464) at W4 and W8, respectively; with median DCV mean-C\textsubscript{trough} of 231 ng/mL (IQR 149-423). In the two patients without SVR12, median DCV mean-C\textsubscript{trough} was 489 ng/mL (IQR 405-84).

A statistically significant correlation was observed between DCV plasmatic exposure and FIB-4: median mean-C\textsubscript{trough} values decreased with increasing FIB-4 values at baseline (rho=-0.35; p=0.037), W4 (rho=-0.44; p=0.008), EOT (rho=-0.40; p=0.023), and after-EOT (rho=-0.39; p=0.028) (Fig. 2, panels a-b).

**Discussion**

The results of our study showed that, in HIV/HCV co-infected patients, plasma concentrations of SOF and of DCV are respectively associated to renal and hepatic function.

On one hand, plasma exposure to the primary metabolite of SOF, GS-331007, that is primarily excreted renally, correlated to kidney function, in terms of
higher concentrations with decreasing eGFR. As this association was not present at baseline and disappeared after DAA treatment, a detrimental effect of SOF treatment on kidney function can be hypothesized.

On the other hand, decreasing DCV plasma concentrations were associated to increasing hepatic impairment as assessed by FIB-4, and this association was found throughout the entire observation period. Besides these observations, no further associations between DAA plasma concentrations and other patient-, treatment-, or disease-related factors were observed.

In our study, lower eGFR during DAA treatment (W4) and at EOT significantly correlated with higher GS-331007 plasma exposure. This finding is in accordance with previous observations that found increase of GS-331007 plasma concentration up to 451% in patients with severe renal damage, leading to possible further nephrotoxicity [8, 13]. In fact, real-life studies suggested higher risk of eGFR deterioration with SOF treatment in patients with preexisting renal impairment, particularly chronic kidney disease, kidney transplant or HIV co-infection [16]. Our study, conducted in patients with overall normal kidney function at baseline, showed mild (within normal range) decline of median eGFR during SOF and DCV treatment, but highlights the association of minor and transitory renal function modifications with SOF metabolite plasma concentrations. The clinical effect of this observation still needs to be assessed, and may be of particular importance in HIV/HCV co-infected patients. In the meanwhile, strict monitoring of renal function during treatment with SOF-based regimens is warranted.

DCV is hepatically metabolized and biliary excretion is the major route of elimination, as it is highly bound to plasma proteins (99%). In cirrhotic patients,
decreased hepatic function impairing metabolic pathways, may lead to lower DCV plasma concentrations [13]. As previously demonstrated and reported in the product information sheet by the European Medicines Agency, among patients with hepatic impairment (Child-Pugh A/B/C) plasma concentrations were lower if compared with unimpaired subjects. Notably, the unbound fraction of DCV remained unchanged in patients with cirrhosis, so that no differences in the active concentration of DCV were found and no need for dose modifications is advised [9-11, 13]. The results of our study were consistent with these observations: decreasing DCV $C_{\text{trough}}$ values were found with increasing severity of hepatic disease.

Even though an association between lower DCV plasma concentrations and slower HCV viral kinetics in HCV mono-infected and HIV/HCV co-infected persons has been reported [17,18], data suggested that the presence of liver impairment has only a limited relevance on DCV pharmacokinetics and, consequently, on its clinical effect [18].

In our study, no apparent effect on the treatment’s virological efficacy was observed but the limited number of subjects failing HCV treatment (only 2 patients) could represent a limitation to this regard.

Furthermore, it is crucial to underscore that achieving sub-optimal DCV drug levels could be an issue for the selection of resistance variants and the choice of future regimen options [19].

From a clinical point of view, our results seem of only limited value since almost 94% of HIV/HCV-coinfected patients treated with a SOF plus DCV, with or without ribavirin, achieved treatment success and both patients with virological treatment failure had $C_{\text{trough}}$ plasma levels in the median values.
Nonetheless, clinical management of HIV/HCV co-infected patients may still need more attention, as accelerated progression of liver fibrosis with higher incidence of cirrhosis and increased frequency of other co-morbid conditions, such as kidney disease, have been reported [20,21].

Latest NS5A inhibitors used in association with SOF (ledipasvir and velpatasvir), which are similarly metabolized by the liver, should be investigated for the same associations.

**Conclusions**

In conclusion, in HIV/HCV co-infected patients treated with SOF plus DCV plasma drug concentrations are associated respectively with renal dysfunction and with liver impairment. Though clinical and therapeutical importance of these findings may apparently be limited, growth of clinicians' knowledge on DAA pharmacokinetic in difficult-to-treat subjects can be relevant in single patients.

**Abbreviations**

BMI, body mass index; ARV, antiretrovirals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DAA, direct-acting antivirals; DCV, daclatasvir; e-GFR, equation for glomerular filtration rate estimate; EOT, end of treatment; FIB-4, Fibrosis 4 score; HCV, hepatitis C virus; IQR, Interquartile range; SOF, sofosbuvir; SVR, sustained virological response; UPLC, Ultra Performance Liquid Chromatography; VAS, visual analogue scale; W, week;

**Declarations section:**
Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki as well as with national and institutional standards. The “Institutional Review Board” of the National Institute for Infectious Disease (local ethics committee) approved the study protocol ("Banca Biologica del Fegato", approval reference number 20/2015). Patients entered the study after receiving the Patient Information and having given written informed consent (version 10, February 3, 2015). All data have been collected anonymously.

Consent to publish

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

Adriana Ammassari (AAm) received speaker’s fees from AbbVie, BMS, Gilead, Janssen Cilag, Merck, ViiV and participated in Advisory Boards for Merck and Janssen; Andrea Antinori (AAn) received personal fees for consultancy and lectures from AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, ViiV and research institutional grants from Bristol Myers Squibb, Gilead, Janssen, ViiV. R. Bellagamba received speaker fees from BMS, Gilead, Janssen Cilag, Merck and ViiV; M. Zaccarelli received speaker grants from AbbVie, Gilead, Merck, Janssen Cilag and ViiV. All other authors: none to declare.
**Funding**

This study was supported by the SIMIT 2015 Scholarship for HIV infection (G Fabbri), the INMI “Lazzaro Spallanzani” Ricerca Corrente grants from the Italian Ministry of Health.

**Authors’ contributions**

Each author participated sufficiently in the work giving substantial contributions to realization;

IM, MT and AAm made contributions to the study conception and design; SN performed therapeutic drug monitoring; GF, RB, AV and MZ contributed to the acquisition of data. PL, FL, the acquisition, analysis and interpretation of data; AAn and CA contributed to the manuscript’s revision. Each author agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

**Acknowledgements**

The authors thank the participants in the study and the nurse staff (Bolzoni L, Ceci O, Parisotto F, Oliva GP) for their permanent support and valuable contribution to the study.
References

1. Navarro J, Laguno M, Vilchez HH, Guardiola JM, Carrion JA, Force L, et al. Efficacy and safety of direct antiviral agents in a cohort of cirrhotic HCV/HIV-coinfected patients. J Antimicrob Chemother. 2017; 72: 2850-6. https://doi.org/10.1093/jac/dkx223.

2. Sikavi C, Chen PH, Lee AD, Saab EG, Choi G, Saab S. Hepatitis C and Human Immunodeficiency Virus Co-Infection in the Era of Direct-Acting Antiviral Agents: No Longer A Difficult to Treat Population. Hepatology 2018; 67: 847-57. https://doi.org/10.1002/hep.29642.

3. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015; 373: 714-25. https://doi.org/10.1056/NEJMoa1503153.

4. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007; 147: 677-84. https://doi.org/10.7326/0003-4819-147-10-200711200-00003.

5. Berenguer J, Rodríguez-Castellano E, Carrero A, Von Wichmann MA, Montero M, Galindo MJ, et al. Eradication of HCV and non-liver-related non-AIDS-related events in HIV/HCV coinfection. Hepatology. 2017; 66: 344-56. https://doi.org/10.1002/hep.29071.
6. EASL Recommendations on Treatment of Hepatitis C 2016 European Association for the Study of the Liver. J Hepatol. 2017; 66: 153-94. https://doi.org/10.1002/hep.29071.

7. EASL Recommendations on Treatment of Hepatitis C 2018 European Association for the Study of the Liver. J Hepatol. 2018; 69: 461-511. https://doi.org/10.1016/j.jhep.2018.03.026.

8. Sovaldi, INN-sofosbuvir – European Medicines Agency – Europa EU http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf

9. Daklinza, INN-daclatasvir – European Medicines Agency – Europa EU http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf

10. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015; 61: 1127-35. https://doi.org/10.1002/hep.27726.

11. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology. 2016; 63: 1493-505. https://doi.org/10.1002/hep.28446.

12. Saeed S, Strumpf EC, Walmsley SL, Rollet-Kurhajec K, Pick N, Martel-Laferrière V, et al. Canadian Co-Infection Cohort Study. How Generalizable Are the Results From Trials of Direct Antiviral Agents to
People Coinfected With HIV/HCV in the Real World? Clin Infect Dis. 2016; 62: 919-26. https://doi.org/10.1093/cid/civ1222.

13. Smolders EJ, de Kanter CT, van Hoek B, Arends JE, Drenth JP, Burger DM. Pharmacokinetics, Efficacy, and Safety of Hepatitis C Virus Drugs in Patients with Liver and/or Renal Impairment. Drug Saf. 2016; 39: 589-611. https://doi.org/10.1007/s40264-016-0420-2.

14. Notari S, Tempestilli M, Fabbri G, Libertone R, Antinori A, et al. UPLC-MS/MS method for the simultaneous quantification of sofosbuvir, sofosbuvir metabolite (GS-331007) and daclatasvir in plasma of HIV/HCV co-infected patients. J Chromatogr B Analyt Technol Biomed Life Sci. 2017; 1073: 183-90. https://doi.org/10.1016/j.jchromb.2017.12.018.

15. Cento V, Nguyen THT, Di Carlo D, Biliotti E, Gianserra L, Lenci I, et al. Improvement of ALT decay kinetics by all-oral HCV treatment: Role of NS5A inhibitors and differences with IFN-based regimens. PLoS One. 2017 18; 12: e0177352. https://doi.org/10.1371/journal.pone.0177352.

16. Faisal N, Bilodeau M, Aljudaibi B, Hirch G, Yoshida EM, Hussaini T, et al. Impact of Sofosbuvir-Based Regimens for the Treatment of Hepatitis C After Liver Transplant on Renal Function: Results of a Canadian National Retrospective Study. Exp Clin Transplant. 2019; 17: 59-63. https://doi.org/10.6002/ect.2017.0201.

17. Virlogeux V, Choupeaux L, Pradat P, Maynard M, Bailly F, Scholtès C, et al. Sofosbuvir plus daclatasvir with or without ribavirin for chronic hepatitis C infection: Impact of drug concentration on viral load decay. DigLiver Dis. 2016; 48: 1351-6. https://doi.org/10.1016/j.dld.2016.07.014.
18. Chan P, Li H, Zhu L, Bifano M, Eley T, Osawa M, et al. Population Pharmacokinetic Analysis of Daclatasvir in Subjects with Chronic Hepatitis C Virus Infection. Clin Pharmacokinet. 2017; 56: 1173-83. https://doi.org/10.1007/s40262-016-0504-2.

19. Parisi SG, Loregian A, Andreis S, Nannetti G, Cavinato S, Basso M, et al. Daclatasvir plasma level and resistance selection in HIV patients with hepatitis C virus cirrhosis treated with daclatasvir, sofosbuvir, and ribavirin. Int J Infect Dis. 2016; 49: 151-3.

20. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001; 33: 562-9. https://doi.org/10.1086/321909.

21. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. Ann Intern Med. 2013; 158: 658-66. https://doi.org/10.7326/0003-4819-158-9-201305070-00604.

Figures legend

Fig. 1
Distribution of sofosbuvir metabolite (GS-331007) mean-Ctrough by CKD-EPI at EOT (A) and by CKD-EPI post EOT (B) using Spearman correlation.

Fig. 2
Distribution of daclatasvir mean-Ctrough by FIB-4 at baseline (A) and by FIB-4 at W4 (B) using Spearman correlation.