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Treatment intensification with boceprevir in HIV-positive patients with acute HCV-genotype 1 infection at high risk for treatment failure

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Summary
Background According to current guidelines, the universal use of direct-acting antiviral agents in HIV-positive patients with acute hepatitis C (AHC) is not recommended. We aimed to evaluate the concept of treatment intensification with boceprevir (BOC) in HIV-positive patients with HCV-genotype 1 AHC (HIV/AHC-GT1) at high risk for failure to pegylated interferon/ribavirin therapy (PEGIFN/RBV).

Methods Nineteen consecutive HIV-positive patients with HIV/AHC-GT1 who underwent antiviral therapy were studied retrospectively.

Patients were treated with PEGIFN/RBV for 24 or 48 weeks, depending on rapid virologic response (RVR; undetectable HCV-RNA at treatment week [W] 4). Patients without complete early virologic response (cEVR; undetectable HCV-RNA at W 12) were offered treatment intensification with BOC at W 12, resulting in 36 weeks of BOC/PEGIFN/RBV triple therapy (total treatment duration: 48 weeks).

Results Thirty-seven percent (7/19) of patients had an RVR and 74 % (14/19) of patients had a cEVR. BOC was used in four out of five patients who did not achieve cEVR and one patient elected to proceed with PEGIFN/RBV.

Sustained virologic response (SVR; undetectable HCV-RNA 24 weeks after the end of treatment) rates were 100 % (14/14) among patients with cEVR treated with PEGIFN/RBV and 75 % (3/4) among patients without cEVR receiving BOC add-on. The patient without cEVR who preferred to continue with PEGIFN/RBV did not achieve SVR. Thus, the overall SVR rate was 89 % (17/19) in intention to treat analysis.

Conclusions BOC add-on in selected HIV/AHC-GT1 resulted in a high overall SVR rate. If 2nd generation direct-acting antiviral agents (DAAs) are not available, treatment intensification with BOC can be considered in HIV/AHC-GT1 at high risk for failure to PEGIFN/RBV.

Keywords Antiviral agents · Human immunodeficiency virus · Hepatitis C · Viral hepatitis · Pegylated interferon alfa-2a · Ribavirin

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Introduction

Liver disease, which is predominately caused by hepatitis C virus (HCV) infection, is the second leading cause of death in patients infected with human immunodeficiency virus (HIV) [1]. HIV/HCV co-infection is observed in 25–30 % of European and American (of USA) HIV-positive patients [2] and was found to be associated with high rates of liver fibrosis progression [3] and markedly higher risks of cirrhosis and end-stage liver disease [4] than HCV mono-infection. In addition, an epidemic of acute hepatitis C (AHC), with an 18-fold increased incidence rate in the past 13 years, has been reported among HIV-positive men who have sex with men (MSM) [5]. This may lead to an additional increase in the prevalence of HIV/HCV

co-infection in the near future, as low rates of spontaneous clearance have been observed among HIV-positive individuals [6]. Thus, effective treatment of AHC in HIV-positive patients is vital.

When compared to AHC in HIV-negative patients, monotherapy with pegylated interferon (PEGIFN) shows moderate efficacy in HIV-positive patients, emphasizing the use of more effective regimens in this patient population. Thus, the European AIDS Treatment Network (NEAT) consensus [7] and the current European AIDS Clinical Society (EACS) guidelines [8] recommend response-guided dual-therapy with PEGIFN plus ribavirin (RBV) for the treatment of AHC in these patients. The majority of previous studies using this regimen reported rates of sustained virologic response (SVR) in the range of 60–80 % [9]. However, in a study by Laguno and coworkers [10], the SVR rate was as low as 47 %. Given the unprecedented advances in the field of chronic hepatitis C therapy in the past years, these SVR rates are no longer satisfying [11].

In 2011, the first-generation HCV protease inhibitors boceprevir (BOC) and telaprevir (TVR) were approved for the treatment of chronic HCV-GT1 infection in combination with PEGIFN/RBV. Results of phase IIa studies of TRV [12] and BOC [13] in combination with PEGIFN/RBV in HIV-positive individuals demonstrated significantly improved efficacy, thereby ushering in a new era in the treatment of chronic HIV/HCV-GT1 co-infection. Moreover, the use of BOC-based response-guided triple-therapy allows for a substantial shortening of treatment duration in the majority of patients with chronic HIV/HCV-GT1 co-infection [14].

In the recently published DAA Based Therapy for Recently Acquired Hepatitis C (DARE-C I) study [15], 12 weeks (up to 24 weeks; the majority of patients were treated for 12 weeks) of TVR-based triple therapy were used in a cohort of HIV-positive patients with AHC co-infected with HCV-GT1 (HIV/AHC-GT1). This approach allowed for reduction of treatment duration and might have increased the rate of SVR (84 %), when compared to PEGIFN/RBV (63 %). Moreover, promising preliminary results from the DAHHS study have been reported [16]. In this study investigating the safety and efficacy of 12 weeks of BOC-based triple therapy in the treatment of HIV/AHC-GT1, 15 out of 16 patients (94 %) had undetectable HCV-RNA at the end of treatment.

However, the use of TVR-/BOC-based triple therapy in unselected HIV/AHC-GT1 might lead to overtreatment of a significant proportion of patients resulting in additional adverse events (AEs) and cost. Thus, according to the current EACS guidelines, the universal use of direct-acting antiviral agent (DAA)-based therapy in HIV-positive patients with AHC is not recommended, although in patients with a lack of virological response to PEGIFN/RBV, treatment intensification with DAAs can be discussed on an individual basis. Importantly, as there is currently no evidence to support this recommendation, a final appraisal of the practicability of this approach has not yet been made.

Thus, we aimed to evaluate the concept of treatment intensification with boceprevir in HIV/AHC-GT1 at high risk of treatment failure.

Patients, materials and methods

Study population

Nineteen consecutive HIV-positive patients with HIV/AHC-GT1 who underwent antiviral therapy at the Medical University of Vienna were studied retrospectively. AHC was diagnosed according to the NEAT consensus [7].

AHC therapy

As recommended by the NEAT consensus [7] and the current EACS guidelines [8], AHC treatment was initiated in patients who did not show a drop in HCV-RNA > 2 $\log_{10}$ IU mL^{-1} at week 4 or who had still detectable HCV-RNA at week 12 after diagnosis. Patients were treated with PEGIFN alfa-2a (Pegasys® [Roche, Vienna, Austria] 180 mcg once weekly) and weight-based RBV (Copegus® [Roche, Vienna, Austria] 1000 or 1200 mg daily) for 24 or 48 weeks, depending on RVR (undetectable HCV-RNA at treatment week 4). Patients without complete early virologic response (cEVR; undetectable HCV-RNA at treatment week [W] 12) were offered treatment intensification with BOC (Victrelis® [Merck Sharp & Dohme, Hoddesdon, UK] 800 mg three times daily) at W 12, resulting in 36 weeks of BOC/PEGIFN/RBV triple therapy (total treatment duration: 48 weeks) (Fig. 1). A simultaneous cART change to tenofovir (TDF)/emtricitabine (FTC)/raltegravir (RAL) was performed in all patients with BOC add-on. SVR was defined as undetectable HCV-RNA 24 weeks after the end of treatment.

Assessed parameters

Epidemiological characteristics were assessed from patients' medical history. Interleukin 28B (IL28B) *rs12979860* SNP genotyping was performed in house using the StepOnePlus Real Time PCR System and a Custom TaqMan SNP Genotyping Assay (Applied Biosystems, Carlsbad, CA, USA), as previously described [17]. HCV genotype was determined using the VERSANT® HCV Genotype 2.0 Assay Line Probe Assay (LiPA) (Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

Liver stiffness measurement

Measurement of liver stiffness was performed by transient elastography (Fibroscan®, Echosens, Paris, France), as previously described [18]. A median by interquartile range ratio ≤ 0.3 was used to define valid measurements

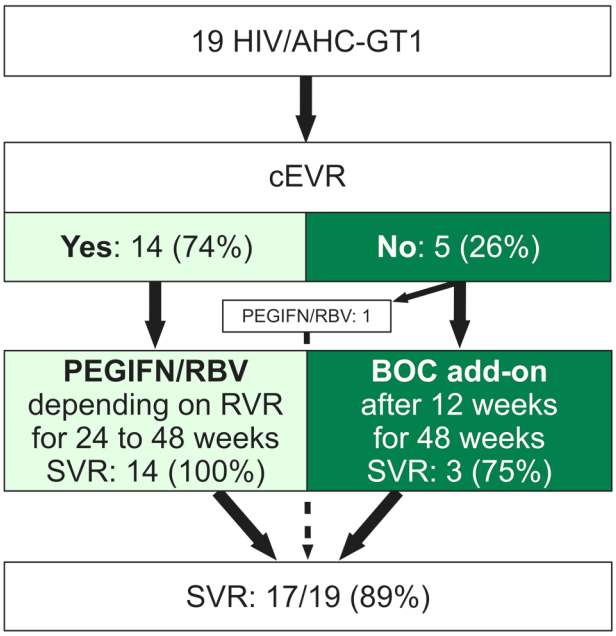

Fig. 1 Seventy-four percent (14/19) of patients had a cEVR. BOC add-on was performed in four out of five patients who did not achieve cEVR, whereas one patient preferred to proceed with PEGIFN/RBV. *cEVR* complete early virologic response, *BOC* boceprevir, *PEGIFN/RBV* pegylated interferon plus ribavirin, *HIV/AHC-GT1* HIV-positive patients with acute hepatitis C co-infected with HCV-genotype 1, *SVR* sustained virologic response

[19]. Advanced liver fibrosis and cirrhosis were defined by liver stiffness values >9.5 kPa and >12.5 kPa, respectively [20].

HCV-RNA testing

HCV-RNA was assessed using the Abbott Real Time HCV assay (Abbott Molecular, Des Plaines, IL, USA) with a lower limit of quantification (LLOQ) and detection of 12 IU/mL.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation or median (interquartile range), whereas categorical variables were reported as number of patients with (proportion of patients with) the certain characteristic.

Ethics

This study was conducted with the understanding and the consent of each participant and in accordance with the declaration of Helsinki as approved by the local ethics committee of the Medical University of Vienna (EKN 1839/2014).

Results

Characteristics of the study population

All patients were men with a mean age of 38.8 ± 8.2 years. The mean CD4 + T-lymphocyte count was 627 ± 244 cells μL^{-1} and 95 % (18/19) of patients were currently on cART. HIV protease inhibitors (PIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), integrase inhibitors (IIs) and nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs) were used in 17 % (3/18), 61 % (11/18), 28 % (5/18) and 94 % (17/18) of patients, respectively. The majority of patients were MSMs (84 % [16/19]), 2 (11 %) patients were infected by intravenous drug use (IDU) and the route of transmission was unknown in one patient (5 % [1/19]). Seventy-nine percent (15/19) of patients were infected with HCV-subtype 1a, while 21 % (4/19) were infected with HCV-subtype 1b. The median HCV-RNA level at the time of initiation of antiviral therapy was 6.16 (2.29) $\log_{10}$ IU mL^{-1}. Fifteen patients (21 %) had the interleukin 28B *rs12979860* SNP (IL28B) non-C/C genotype and the median liver stiffness prior to the initiation of PEGIFN/RBV therapy was 6.9 (5.5) kPa. Liver stiffness values >9.5 kPa and >12.5 kPa were observed in 26 % (5/19) and 11 % (2/19) of patients, respectively. At the time of liver stiffness measurement, the median serum bilirubin level was 0.78 (0.58) mg/dL. The mean serum asparate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) levels were 126 ± 87, 257 ± 211 and 202 ± 141 U/L, respectively.

Rates of RVR and cEVR

Thirty-seven percent (7/19) of patients had a RVR, and 74 % (14/19) of patients had a cEVR (Fig. 1). BOC add-on was performed in four out of five patients who did not achieve cEVR (Table 1), whereas one patient preferred to proceed with PEGIFN/RBV.

Characteristics of patients with BOC add-on

In four patients without cEVR to PEGIFN/RBV therapy, BOC was added at W 12. At the time of initiation of PEGIFN/RBV therapy, all patients had well-preserved CD4+ T-lymphocyte counts ranging from 441 to 1295 cells μL^{-1}, and all patients were on cART. Three patients received TDF/FTC/EFV, and one patient was on TDF/FTC/DRV/r. The liver stiffness values at the time of diagnosis were 8.4, 21.3, 7.8, and 35.3 kPa in patients A, B, C, and D, respectively. All patients were infected with HCV-subtype 1a and had the IL28B C/T genotype.

Table 1 Characteristics of the four patients with BOC add-on

Patient characteristics	Patient A	Patient B	Patient C	Patient D
HIV infection parameters				
CD4 + T-lymphocyte count (cells μL^{-1})	441	1295	580	575
cART at baseline	TDF/FTC/EFV	TDF/FTC/EFV	TDF/FTC/EFV	TDF/FTC/DRV/r
cART at BOC add-on	TDF/FTC/RAL	TDF/FTC/RAL	TDF/FTC/RAL	TDF/FTC/RAL
HCV infection parameters				
HCV subtype	1a	1a	1a	1a
HCV-RNA (log IU mL^{-1})	6.65	6.97	6.75	6.53
IL28B genotype	C/T	C/T	C/T	C/T
Pre-treatment liver stiffness (kPa)	8.4	21.3	7.8	35.3
Post-treatment liver stiffness (kPa)	4	16.3	4.1	14
HCV-RNA (log IU mL^{-1})				
W 4	5.94	6.24	6.68	6.18
W 8	5.85	3.69	4.16	6.18
W 12	4.87	2.68	3.31	6.18
4 weeks after BOC add-on (W 16)	Undetectable	Undetectable	Undetectable	2.25
8 weeks after BOC add-on (W 24)	Undetectable	Undetectable	Undetectable	< LLOQ
W 24	Undetectable	Undetectable	Undetectable	Undetectable
W 48	Undetectable	Undetectable	Undetectable	6.1
FU12	Undetectable	Undetectable	Undetectable	SOF/DCV[a]
FU24	Undetectable	Undetectable	Undetectable	SOF/DCV[a]

cART combined antiretroviral therapy, *TDF/FTC/EFV* tenofovir/emtricitabine/efavirenz, *TDF/FTC/DRV/r* tenofovir/emtricitabine/darunavir/ritonavir, *TDF/FTC/RAL* tenofovir/emtricitabine/raltegravir, *HCV* hepatitis C virus, *BOC* boceprevir, *IL28B* Interleukin 28B *rs12979860* SNP, *W* treatment week, *FU* follow-up week
[a]Patient D was retreated with sofosbuvir (SOF)/daclatasvir (DCV). HCV-RNA was < LLOQ after 8 weeks and undetectable after 12 weeks of SOF/DCV. The patient was treated for 24 weeks and achieved a SVR

Treatment course and outcome of patients with BOC add-on

Prior to the add-on of BOC, cART was switched to TDF/FTC/RAL in all patients. HCV-RNA levels at the time of BOC add-on (W 12) were 4.87, 2.68, 3.31 and 6.18 $\log_{10}$ IU mL^{-1} in patients A, B, C and D, respectively (Fig. 2). Three out of four (75 %) patients had undetectable HCV-RNA 4 weeks after the add-on of BOC, and all of these patients had an SVR (Table 1). In contrast, one patient still had detectable HCV-RNA (< LLOQ) 8 weeks after the add-on of BOC (W 16), became undetectable 12 weeks after the add-on of BOC (W 24) and finally had a virological breakthrough (patient D) (Fig. 2).

Interestingly, while liver stiffness decreased to normal values in patients A and C, it remained in the range suggestive for cirrhosis in patients B and D. Patients B and D were diagnosed with coexisting non-alcoholic fatty liver disease and alcoholic liver disease, respectively.

All patients had at least one AE, while no serious AEs or treatment discontinuations due to AEs occurred. Patients A, C and D received granulocyte colony-stimulating factor analogues. Administration of erythropoietin analogues or RBV dose reduction was necessary in all four patients, whereas none of the patients received blood transfusions.

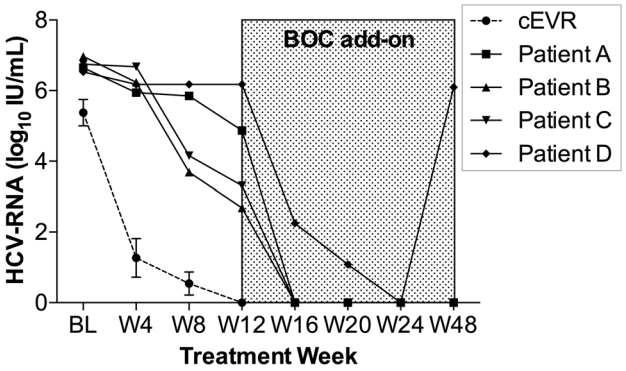

Fig. 2 Viral kinetics in patients with cEVR treated with PEGIFN/RBV and four patients without cEVR receiving BOC add-on (*patients A, B, C and D*). The fifth patient not achieving cEVR who elected to proceed with PEGIFN/RBV is not shown. Statistics: Symbols indicate the mean, whereas error bars display the standard error of the mean. *cEVR* complete early virologic response, *PEGIFN/RBV* pegylated interferon plus ribavirin, *BOC* boceprevir, *W* treatment week

Patient D was retreated with sofosbuvir (SOF)/daclatasvir (DCV). HCV-RNA was < LLOQ after 8 weeks and undetectable after 12 weeks of SOF/DCV. The patient was treated for 24 weeks and achieved a SVR.

Table 2 Characteristics of the study population

Patient characteristics	
Age	38.8 ± 8.2
Sex, male	100 % (19/19)
HIV infection parameters	
CD4 + T-lymphocyte count (cells μL^{-1})	627 ± 244
cART	95 % (18/19)
cART drugs	
PI	17 % (3/18)
NNRTI	61 % (11/18)
II	28 % (5/18)
NRTI	94 % (17/18)
HCV infection parameters	
Route of transmission	
MSM	84 % (16/19)
IDU	11 % (2/19)
Unknown	5 % (1/19)
HCV subtype	
1a	79 % (15/19)
1b	21 % (4/19)
HCV-RNA (log IU mL^{-1})	6.16 (2.29)
IL28B genotype	
C/C	21 % (4/19)
Non-C/C	79 % (15/19)
Liver stiffness (kPa)	6.9 (5.5)
> 9.5 kPa	26 % (5/19)
> 12.5 kPa	11 % (2/19)

cART combined antiretroviral therapy, *PI* HIV protease inhibitor, *NNRTI* non-nucleoside reverse-transcriptase inhibitors, *II* integrase inhibitors, *NRTI* nucleoside/nucleotide reverse-transcriptase inhibitors, *HCV* hepatitis C virus, *MSM* men who have sex with men, *IDU* intravenous drug use, *IL28B* Interleukin 28B *rs12979860* SNP

Treatment outcome of patients with PEGIFN/RBV

Among patients with cEVR, duration of PEGIFN/RBV treatment was 24 weeks in 50 % (7/14) of patients, whereas 50 % (7/14) were treated for 48 weeks. All patients had an SVR (Fig. 1). Viral kinetics of this subgroup are shown in Fig. 2. In the patient without cEVR who preferred to continue with PEGIFN/RBV, treatment was discontinued due to AEs at treatment W 16. This patient did not achieve SVR.

Overall rates of SVR

In summary, SVR rates were 100 % (14/14) among patients with cEVR treated with PEGIFN/RBV and 75 % (3/4) among patients without cEVR receiving BOC add-on. The patient without cEVR who preferred to continue with PEGIFN/RBV did not achieve SVR. Thus, the overall SVR rate was 89 % (17/19) in intention to treat analysis.

Conclusions

Recently, Doward and co-workers [9] reported SVR rates as high as 91 % in a cohort of patients treated according to the NEAT consensus. However, the majority of these patients had a rapid virologic response (RVR) and only 13 % did not achieve cEVR. Thus, it might be concluded that the high rates of SVR in HIV-positive patients with AHC are primarily based on the rapid decline in viral load observed in the majority of patients. This hypothesis is further supported by unpublished results from the NEAT cohort, composed of 209 HIV-positive patients with HIV/AHC-GT1. Although excellent SVR rates of 85 % were observed among patients with cEVR, SVR rates among patients with partial early virologic response or null response were as low as 18 and 0 %. Thus, more effective treatment regimens are clearly required for these two subgroups of patients.

The recently published DARE-C I study [15] and a first report from the DAHHS study [16] have shown promising results with a shortened duration of TVR-/BOC-based triple therapy in HIV/AHC-GT1. However, current EACS guidelines [8] warn against the universal use of these regimens, as it might lead to an overtreatment of a significant proportion of patients resulting in additional AEs and cost. Serious AEs are of particular concern when using first-generation HCV protease inhibitors in HIV-positive patients. In the HIVCOBOC-RGT study [14], SAEs related to bacterial infections and requiring treatment discontinuation were observed in 2 out of 21 patients. In addition, three cases of nonserious AEs due to bacterial infection were documented in this study. Importantly, all of these patients had a preserved immune status, suppressed HIV-RNA and did not have liver cirrhosis. Thus, HIV-positive patients might show high susceptibility for severe infectious complications during BOC-based triple therapy. This finding is not limited to patients with cirrhosis and additional risk factors [21, 22]. In the current study, no SAEs or treatment discontinuations occurred, although two patients had cirrhosis. However, the significance of this observation is limited by the small sample size.

In our study, the add-on of BOC in patients at high risk for treatment failure resulted in a SVR in three out of four patients, including a patient with null response to PEGIFN/RBV and a patient with pre-existing cirrhosis of non-viral aetiology. However, this regimen was not effective in another patient with both pre-existing cirrhosis and a null response to PEGIFN/RBV. Thus, this patient who initially presented as 'easy to cure' patient with AHC, ended up being a PEGIFN/RBV null-responder and first-generation HCV protease inhibitor failure with chronic HIV/HCV-GT1 co-infection and cirrhosis. Retreatment with SOF/DCV was successful, which is in line with the encouraging results in patients with chronic HCV-GT1 mono-infection, advanced liver fibrosis and first-generation DAA failure [23].

Surprisingly, in our study, 2 out of 19 patients with AHC had confirmed cirrhosis of other aetiology, high-

lighting the urgent need for second-generation DAAs, even in these presumably 'easy to cure' patients. IFN-based [24] and IFN-free [25–30] regimens have not only been highly effective but are also generally well-tolerated in the setting of chronic HIV/HCV co-infection. Results of ongoing studies investigating the use of 6 to 12 weeks of sofosbuvir (SOF)/RBV (DARE-C II and SWIFT-C study), or 6 weeks of SOF/ledipasvir (SOL study) in the setting of AHC are highly anticipated [16]. However, health insurance providers in many European countries currently restrict the access to second-generation DAAs to patients with advanced liver fibrosis for economic reasons. This is of particular concern in patients with AHC, as parallel to the normalization of liver enzymes, liver stiffness decreases to normal values in the majority of patients.

Although a high overall SVR rate was observed in our study, treatment duration is still in the range of 24–48 weeks. However, it is unclear whether benefits of shortening treatment duration to 12 weeks outweigh the additional side affects arising from the universal use of TRV or BOC in the DARE-C I [15] or the DAHHS study [16], respectively.

In conclusion, BOC add-on in selected HIV/AHC-GT1 resulted in a high overall SVR rate. If second-generation DAAs are not available, treatment intensification with BOC can be considered in HIV/AHC-GT1 at high risk for failure to PEGIFN/RBV. Interestingly, two out of 19 patients with AHC had confirmed cirrhosis of other aetiology, highlighting the urgent need for second-generation DAAs and IFN-free regimens, even in these presumably 'easy to cure' patients.

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Conflict of interest
Mattias Mandorfer received grants from the Medical Scientific Fund of the Major of the City of Vienna, honoraria for consulting from Janssen, payments for lectures from Boehringer Ingelheim, Bristol-Myers Squibb, Janssen and Roche, as well as travel support from AbbVie, MSD and Roche.

Philipp Schwabl received payments for lectures from Roche and travel support from Janssen and Roche.

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Michael Trauner received grants from MSD, honoraria for consulting from AbbVie, Gilead, Janssen and MSD, payments for lectures from Gilead, MSD and Roche as well as travel support from Gilead.

Thomas Reiberger received payments for lectures from Roche, as well as travel support from Gilead, MSD and Roche.

Markus Peck-Radosavljevic received grants from Gilead, MSD and Roche, honoraria for board membership and consulting from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen and MSD, as well as payments for lectures from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, MSD and Roche.

For the remaining authors none were declared.

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