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Interferon-free therapy in hepatitis C virus (HCV) monoinfected and HCV/HIV coinfected patients: effect on cognitive function, fatigue, and mental health

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Abstract

The efficacy and safety of interferon-free therapies for hepatitis C virus (HCV) infection have been reported. Considering the accumulating evidence for a direct central nervous system infection by HCV, we aim to evaluate the effect of direct acting antivirals (DAA) therapy on cognitive function in HCV patients. We conducted a longitudinal analysis of the cognitive performance of 22 patients (8 HCV+, 14 HCV+/HIV+) who completed neuropsychological testing at baseline and at week 12 after DAA therapy. In 20 patients, we analyzed specific attention parameters derived from an experimental testing based on the Theory of Visual Attention (TVA). Depression, fatigue, and mental health were assessed as patient reported outcomes. At baseline, 54.5% of the patients met the criteria for cognitive impairment and 40% showed impairment in TVA parameters. Follow-up analysis revealed significant improvements in the domains of visual memory/learning, executive functions, verbal fluency, processing speed, and motor skills but not in verbal learning and attention/working memory. We did not observe significant improvement in visual attention measured by TVA. Fatigue and mental health significantly improved at follow-up. Our findings indicate that successful DAA treatment leads to cognitive improvements in several domains measured by standard neuropsychological testing. The absence of improvement in TVA parameters and of significant improvement in the domain of attention/working memory might reflect the persistence of specific cognitive deficits after HCV eradication. In summary, DAA treatment seems to have a positive effect on some cognitive domains and leads to an improvement in mental health and fatigue in HCV-infected patients.

Keywords Clinical trial · Cognitive dysfunction · Direct acting antivirals · Hepatitis C virus · Neuropsychological assessment · Theory of Visual Attention

Felix Kleefeld and Sophie Heller contributed equally to this work

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Introduction

With the emergence of new interferon-free therapies for the treatment of chronic hepatitis C virus (HCV) infections, the therapeutic options for infected patients profoundly changed. Phase III studies (e.g., Afdhal et al. (2014)) and real-world cohorts (Ingiliz et al. 2016; Sulkowski et al. 2016) showed comparable highly sustained virological response (SVR) rates and low rates of side effects from direct acting antivirals (DAAs). As the efficacy and safety of DAAs have been documented, it is now possible to focus on specific aspects such as central nervous system (CNS) manifestations caused by HCV. Numerous studies have investigated the occurrence of cognitive deficits in HCV patients. Due to the detection of cognitive impairment in HCV patients with only mild liver disease, the hypothesis of a direct CNS infection by HCV—

independently of hepatic encephalopathy—evolved (Forton et al. 2001). Neuroinflammatory processes in HCV patients have been documented by imaging studies showing altered metabolism in certain brain areas (Forton et al. 2008; Weissenborn et al. 2004), microglial activation (Grover et al. 2012; Pflugrad et al. 2016), microstructural brain abnormalities (Thames et al. 2015), or cerebral microcirculation changes (Bladowska et al. 2014). Similar alterations are found in patients infected with the human immunodeficiency virus (HIV) (Anderson et al. 2015; Hammoud et al. 2005). Besides the detection of negative stranded HCV-RNA in autopsy brain tissues (Radkowski et al. 2002), in vivo detection of viral variants in the cerebrospinal fluid (CSF) of two cognitively impaired patients could recently be shown (Tully et al. 2016). As the brain endothelium cells exhibit all receptors necessary for a direct entrance of the HCV (Fletcher et al. 2012), a CNS infection seems to be likely. The resulting neuroinflammatory processes may be the cause for neuropsychiatric implications like fatigue and cognitive deficits in HCV patients (Grover et al. 2012; Thames et al. 2015). A HCV coinfection might even increase the extent and frequency of cognitive deficits in HIV patients (Hinkin et al. 2008; Vivithanaporn et al. 2012). As these symptoms are compromising for the patients, the question of reversibility after HCV eradication is of notable importance. Fatigue and health-related quality of life are aspects that have already been investigated and existing research suggests an improvement after DAA treatment (Gerber et al. 2016; Younossi et al. 2014). However, several studies targeting the issue of reversibility of cognitive deficits after HCV eradication resulted in controversial results. Kraus et al. (2013) found significant cognitive improvement of responders to antiviral therapy compared to non-responders, and Cattie et al. (2014) stated therapy-induced and persistent cognitive decline. Huckans et al. (2015) reported no changes of cognitive functions during and following an interferon-based treatment; however, SVR was associated with lower fatigue levels and depression scores. A recent study suggested cognitive improvement in a subgroup of responders to antiviral HCV therapy, associated with positive changes in white matter integrity (Kuhn et al. 2017). Of note is that these studies are based on the former standard interferon-based therapy, which is known to have a high burden of psychiatric side effects like depression and cognitive impairment itself (Reichenberg et al. 2005). To achieve reliable insights into this matter it is necessary to assess cognitive functions of carefully selected HCV monoinfected and HCV/HIV coinfected patients before and after a DAA therapy, considering hepatic impairment, neurologic or psychiatric comorbidity, and substance dependency.

We recently reported preliminary data indicating an improvement of cognitive functions after a DAA therapy using a standard neuropsychological test battery (Kleefeld et al. 2017). We now report complete follow-up data of our patient cohort. In addition, this includes data of a subgroup of patients who underwent experimental testing of distinct visual attentional parameters. In this subgroup, we applied an experimental paradigm based on the Theory of Visual Attention (TVA (Bundesen 1990)). We chose this approach, because TVA has been shown to be a sensitive instrument for the detection of attentional deficits in different neurological disorders (e.g., mild cognitive impairment and Alzheimer's disease, see Bublak et al. (2011), Huntington's disease (Finke et al. 2006), thalamic stroke (Kraft et al. 2015)) and has good psychometric properties (Habekost et al. 2014). We expected a significant improvement of cognitive functioning measured by comprehensive neuropsychological testing and TVA-based testing after HCV eradication. Correspondingly, we expected improvements in self-reported parameters such as fatigue, mental health, and depression.

Methods

Patients and the control group

We recruited HCV monoinfected and HCV/HIV coinfected patients in three medical cabinets in Berlin ((1) Center for Infectiology Berlin, (2) Praxis Jessen, (3) MVZ for Gastroenterology Bayerischer Platz). HCV patients who underwent interferon-free DAA treatment were invited to participate in the study. Inclusion criteria were chronic viraemic HCV infection (detection of HCV-antibodies (ELISA) and HCV-RNA (PCR), present for at least 6 months) and controlled HIV infection for coinfected patients, which was defined as being under stable combined antiretroviral therapy (cART) for at least 3 months and having an undetectable viral load in the preceding two measurements (measurement interval 3 months). Exclusion criteria were liver cirrhosis (defined as liver stiffness ≥ 12.5 kPa measured by transient elastography (Fibro Scan®)), chronic hepatitis B infection, any current or past neurologic or severe psychiatric disease, active or recent drug or alcohol abuse, or any opiate replacement therapy.

For conventional neuropsychological testing, a healthy control group was assessed only for baseline. The control group did not differ significantly from the patient group concerning age, education, and intelligence level (data already reported (Kleefeld et al. 2017)).

For TVA-based assessment, a separate control group of healthy subjects matched for age, gender, education, and intelligence was recruited. Participants received financial compensation (30 euros) for their participation. Both control groups fulfilled the following criteria: no HCV or HIV infection or other liver disease, no evidence of neurological, psychiatric or ophthalmological pathology, no active/recent or past alcoholism or drug abuse, and no intake of medication affecting the central nervous system.

The study followed the ethical principles of the World Medical Association (Declaration of Helsinki) and was approved by the local ethical research committee (reference number: EA1/153/14). Written informed consent was obtained from each participant included in the study.

Procedure

After inclusion in the study, every patient underwent neuropsychological testing and a subgroup of patients completed TVA-based testing (TVA patient subgroup). Additionally, the patients were asked for self-reported cognitive complaints like forgetfulness, difficulties with thinking, problem solving, sustained attention/concentration, and completed questionnaires for depression (Beck's Depression Inventory-Fast Screen (BDI-FS) (Beck et al. 2000)), fatigue (Fatigue Severity Scale (FSS) (Rosa et al. 2014)), and health-related quality of life (Short Form 12 (SF-12) (Gandek et al. 1998; Ware et al. 1996)) at baseline and follow-up.

The patients' performance at baseline was evaluated before beginning an 8- or 12-week interferon-free treatment. A follow-up assessment was conducted 12 weeks after therapy completion. To reduce time-of-day effects, both testing sessions were scheduled for the same time of day whenever possible. Control subjects for the TVA-based testing (TVA control group) were equally tested twice within the same test-retest interval of 20–24 weeks.

Laboratory data were received from the medical files, considering the closest date to the testing sessions at baseline and follow-up (see Table 1).

Neuropsychological testing

Patients completed a comprehensive neuropsychological test battery including ten different tests covering eight cognitive domains at each visit (see Table 2), as already specified in part (Kleefeld et al. 2017), and comprising the following tests: Rey-Osterrieth Complex Figure Test (ROCF) (Strauss et al. 2006), Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span Subtest (von Aster et al. 2006a), d2 Test of attention (Brickenkamp et al. 2010), Color Word Interference Test (Stroop) (Bäumler 1985), Trail Making Test Part A and B (Reitan 1979), Verbaler Lern- und Merkfähigkeitstest (VLMT) (Helmstaedter et al. 2001), Regensburger Wortflüssigkeitstest (RWT) (Aschenbrenner et al. 2001), WAIS-III Digit-Symbol Subtest (von Aster et al. 2006b), Grooved Pegboard Test (Trites 2002), and Horn's Performance Test System Subtest 3 (Leistungsprüfsystem (LPS)) (Horn 1983).

Test selection was based on international recommendations for the evaluation of cognitive deficits in patients with HIV-associated neurocognitive disorder (HAND) (Antinori et al. 2007). The completion of neuropsychological testing took between 1 1/2 and 2 h. Testing was guided by the same researcher for baseline and follow-up. To minimize practice effects, we used parallel test versions for follow-up if available.

Table 1 Demographic characteristics and questionnaire scores of the patient group (HCV monoinfected and HCV/HIV coinfected patients)

	Baseline Mean (SD)	Follow-up Mean (SD)	*p* value
HCV viral load (copies/mL)	2,852,491.82 (4,721,243.46) ($n = 22$)		–
AST (IU/L)	62.71 (50.89) ($n = 21$)	25.15 (9.77) ($n = 20$)	–
ALT (IU/L)	95.18 (90.49) ($n = 22$)	22.24 (16.97) ($n = 21$)	–
Bilirubin (mg/dL)	0.83 (0.80) ($n = 21$)	0.71 (0.66) ($n = 20$)	–
INR	1.04 (0.12) ($n = 15$)	1.02 (0.03) ($n = 9$)	–
Albumin (g/L)	45.86 (4.36) ($n = 21$)	46.64 (5.12) ($n = 10$)	–
Platelets/nL	221.09 (52.98) ($n = 22$)	234.90 (43.15) ($n = 21$)	–
Current CD4+ cell count/μL (only HIV+/HCV+ patients)	841.50 (250.38) ($n = 14$)	814.77 (222.61) ($n = 13$)	–
Depression[a]	1.76 (1.37)	2.10 (2.57)	$t(20) = -0.598$, $p = .557$
Fatigue[b]	4.47 (1.62)	3.75 (1.83)	$t(20) = 2.347$, $p = .029$*
SF-12 physical sum scale[c]	50.76 (8.10)	52.81 (8.21)	$t(20) = -1.231$, $p = .233$
SF-12 psychic sum scale[c]	38.60 (12.19)	45.02 (10.54)	$t(20) = -3.086$, $p = .006$**

[a] BDI-FS score [b] FSS score [c] SF-12 scores ($n = 21$, one patient did not complete the questionnaires at follow-up). Not every laboratory value was available for all patients and/or time points, so the number of patients varies depending on the value. *Significant at the $p < .05$ level. **Significant at the $p < .01$ level

Table 2 Results of the neuropsychological test battery (HCV monoinfected and HCV/HIV coinfected patients)

Domains evaluated	Baseline ($n = 22$)	Follow-up ($n = 22$)	Test statistic, p value
Visual learning/memory			
ROCF: immediate recall	51.60 (12.01)	67.69 (8.01)	$t(21) = -8.392$, $p = .000$**
ROCF: delayed recall	50.39 (11.25)	66.83 (7.50)	$t(21) = -8.888$, $p = .000$**
Attention/working memory			
Digit span: forwards	50.09 (11.89)	53.20 (12.83)	$t(21) = -1.976$, $p = .061$
Digit span: backwards	51.00 (10.84)	53.15 (10.54)	$t(21) = -1.396$, $p = .177$
d2 test of attention: concentration	44.36 (8.26)	46.95 (5.40)	$t(21) = -2.051$, $p = .053$
Executive functions			
Color-Word-Interference Test (Stroop)	48.41 (11.27)	53.86 (11.85)	$t(21) = -2.806$, $p = .011$*
Trail Making Test Part B	48.88 (13.11)	54.30 (10.58)	$t(21) = -3.102$, $p = .005$**
Learning and recall—verbal memory			
VLMT: total recall	55.68 (8.16)	54.84 (7.33)	$t(21) = 0.587$, $p = .564$
VLMT: immediate recall	50.77 (9.30)	53.84 (10.51)	$t(21) = -1.439$, $p = .165$
VLMT: delayed recall	52.85 (8.10)	54.56 (9.37)	$t(21) = -0.796$, $p = .435$
VLMT: Recognition trial	54.03 (11.42)	57.78 (7.06)	$t(21) = -2.000$, $p = .059$
Verbal fluency			
RWT, subtest S-/T-words	49.85 (10.57)	49.55 (8.75)	$t(21) = 0.182$, $p = .857$
RWT, subtest animals	49.28 (13.09)	53.40 (12.08)	$t(21) = -2.753$, $p = .012$*
Processing speed			
Trail Making Test Part A	48.27 (10.76)	54.40 (13.48)	$t(21) = -3.535$, $p = .002$**
WAIS-III, Subtest Digit Symbol-Coding	47.44 (6.24)	50.02 (7.05)	$t(21) = -2.787$, $p = .011$*
Motor skills			
Grooved Pegboard Test	65.18 (6.86)	61.91 (7.26)	$t(21) = 3.542$, $p = .002$**
Non-verbal intelligence level			
Horn's Performance Test System (LPS), subtest 3	57.18 (8.99)	–	–

Values are presented as mean (SD) of T-scores for all tests except Grooved Pegboard (raw score in seconds (SD))

ROCF Rey/Osterrieth Complex Figure Test, *VLMT* Verbaler Lern- und Merkfähigkeitstest, *RWT* Regensburger Wortflüssigkeitstest, *WAIS-III* Wechsler Adult Intelligence Scale-Third Edition, *LPS* Leistungsprüfsystem

*Significant at the $p < .05$ level; **significant at the $p < .01$ level

TVA-based testing

We used the computer-based CombiTVA paradigm as published by Vangkilde et al. (2011). A testing session comprised of nine blocks made up of 36 single trials and took 45 min to complete. The basic design of a trial is illustrated in Suppl. Fig. 1. The paradigm consists of whole report trials with two or six red target letters displayed on the screen for various durations and of partial report trials with two red target and four blue distractor letters presented on the screen. The participant always had to report as many *red* letters as he or she had seen. The resulting number of correctly reported letters in each trial served as the main dependent variable.

Five parameters of visual attention were estimated by applying a maximum likelihood fitting procedure (Dyrholm et al. 2011): (1) K, the capacity of visual short-term memory (number of letters; 5 degrees of freedom [*df*]); (2) C, the visual processing speed (letters per second; 1 *df*); (3) t_0, the perceptual threshold or the longest ineffective exposure duration (in milliseconds; 1 *df*); (4) α, the top-down controlled selectivity (a value close to 0 represents good selectivity, a value close to 1 indicates rather ineffective prioritization of targets compared to distractors; 1 *df*); and (5) w_{index}, the spatial distribution of attentional weighting, allowing the detection of an attentional bias to the left or right hemifield (5 *df*).

The fitting of one patient was based on 32 fewer trials than the other patients (292 instead of 324) because of the early termination of the testing session due to technical issues during the last trial block. For participants with an initial negative t_0 estimate, the fitting was rerun with a protocol fixing t_0 to zero. Supplementary Figs. 2 and 3 provide additional visualization of the parameters K, C, t_0, and α.

Statistical analysis

Neuropsychological testing and questionnaires

The patients' raw scores were converted to demographically (age and education) corrected T-scores. As no corrected T-scores were available for the Grooved Pegboard Test, we used the raw scores to assess for longitudinal changes.

To analyze baseline differences between the control and the patient group (and between mono- and coinfected patients), we performed *t* tests for independent samples. For the exploration of pre-post changes of neuropsychological performance, we used *t* tests for dependent samples. To assess for differences in therapy effects between mono- and coinfected patients, we used a mixed-measure analysis of variance (ANOVA) with the within-subject factor "treatment status" (pre-treatment, post-treatment) and the between-subject factor "infection status" (monoinfected, coinfected).

For the pre-post comparison of FSS, BDI-FS, and SF-12 scores in the patient group, we used *t* tests for dependent samples.

To correlate fatigue, depression, and health-related quality of life with neuropsychological test results, we used bivariate Pearson's correlations.

As in our previous study (Kleefeld et al. 2017), results were considered significant at $p \leq .05$.

TVA-based testing

Demographical data and baseline differences in estimated TVA parameters between the TVA patient subgroup and the TVA control group were analyzed by *t* tests for independent samples.

To evaluate the individual performance of each patient, we considered the mean and standard deviation (SD) (of baseline and follow-up data, respectively) of the control group as demographically adjusted norms, for each TVA parameter, respectively. We classified a patient as impaired if he performed more than one SD below the control group's mean in ≥ 1 TVA parameter. This approach is based on the recommended criteria for cognitive impairment in HIV patients (Antinori et al. 2007).

To compare the pre-post performance changes between the patient and the control group, we conducted mixed-measure ANOVAs with the within-subject factor "time" (baseline, follow-up) and the between-subject factor "group" (patient group, control group). Additionally, dependent *t* tests were used to test for within-group differences between baseline and follow-up. For subgroup analysis between mono- and coinfected patients, we conducted mixed-measure ANOVAs with the within-subject factor time (baseline, follow-up) and the between-subject factor infection status (monoinfected, coinfected).

Some TVA parameters (C,α, and t_0) violated the assumption of normality. As *t* tests are assumed to be robust against violations to their assumptions (Boneau 1960), we nonetheless decided to conduct all analyses with parametric methods.

Almost all participants had normal or corrected-to-normal vision. One patient had a deuteranomaly measured by Ishihara's color perception test (Ishihara 1976). As he might have been compromised in the partial report trials (where the participant has to distinguish between letters differing in color), the main analyses concerning the partial report trials (α, w_{index}) were additionally conducted excluding this patient, to verify if the results hereby changed.

Results

Clinical characteristics

Overall, 206 patients were started on DAA treatment at the first two sites between March 2015 and April 2016. Of those who fulfilled the study criteria, 23 agreed to participate in the study. Two additional patients were recruited at the third site. From a total of 25 patients, 22 completed the study (21 male and one female) of whom 14 were coinfected with HIV (Fig. 1).

Modes of HCV infection were men who have sex with men (MSM) ($n = 12$), former intravenous drug use ($n = 5$), transfusion of blood products ($n = 3$), and others/unknown ($n = 2$). 81.8% ($n = 18$) of the patients were infected with genotype 1 and 18.2% ($n = 4$) with genotype 4.

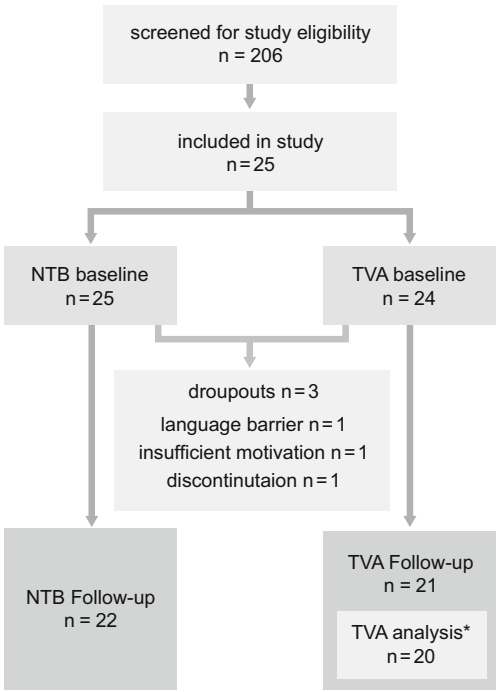

Fig. 1 Study flowchart. NTB Neuropsychological Test Battery. *One patient was excluded, as the TVA model was not well applicable to his data

Treatment regimens were Ledipasvir/Sofosbuvir ($n = 16$), Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir + Ribavirin ($n = 1$), Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir ($n = 1$), Ombitasvir/Paritaprevir/Ritonavir + Ribavirin ($n = 2$), Sofosbuvir + Ribavirin ($n = 1$), or Simeprevir + Sofosbuvir + Ribavirin ($n = 1$) for either 8 or 12 weeks. Seven patients were previously treated with interferon-based regimens.

Twenty-one of the 22 patients had an undetectable HCV RNA 12 weeks after the end of treatment (SVR 12). One patient exhibited a relapse at week 12 after therapy after initial HCV clearance, and one patient discontinued his therapy at week 4 because of comorbid myocardial infarction; nevertheless, he had a SVR 12. Both patients were kept in the analysis. In general, the therapy regimens were well tolerated. Side effects were reported by 10 patients, comprising fatigue ($n = 4$), skin affection ($n = 3$), nausea ($n = 2$), headache ($n = 1$), sleep disturbance ($n = 1$), and concentration disturbance ($n = 1$).

The demographic characteristics of the complete patient group are shown in Table 1. The coinfected patient group ($n = 14$) did not differ significantly from the HCV monoinfected group ($n = 8$) with respect to demographic and laboratory data (HCV+/HIV+ [mean age 42.14 (SD 10.87), mean education years 15.43 (SD 2.38), mean IQ 110.43 (SD 14.90), mean viral load 3,927,928.57 copies/mL (SD 5,663,153.94), mean AST 72.00 IU/L (SD 59.82), mean ALT 112.21 IU/L (SD 108.83), mean platelets/nL 226.50 (SD 45.00), mean bilirubin 0.98 mg/dL (SD 0.95), mean INR 1.06 (SD0.14) ($n = 9$), mean albumin 45.64 g/L (SD 4.00)]; HCV+ [mean age 44.00 (SD 13.53), mean education years 14.50 (SD 2.33), mean IQ 111.38 (SD 11.54), mean viral load 970,477.50 copies/mL (SD 973,810.71), mean AST 44.14 IU/L (SD 16.62) ($n = 7$), mean ALT 65.38 IU/L (SD 31.25), mean platelets/nL 211.63 (SD 67.08), mean bilirubin 0.56 mg/dL (SD 0.21) ($n = 7$), mean INR 1.00 (SD 0.06) ($n = 6$), mean albumin 46.30 g/L (SD 5.33) ($n = 7$)]; all $p > .05$).

Twenty-four of the 25 patients agreed to participate in optional TVA-based testing. Twenty-one patients completed baseline and follow-up testing, 20 patients (19 male and one female; 12 HIV/HCV coinfected) were included in the final analysis of CombiTVA results (see Fig. 1). Forty-two healthy subjects were recruited for the TVA control group. Four were not contactable anymore for follow-up, one was excluded subsequently (due to former alcohol abuse), two discontinued their participation. The final analysis comprised 35 controls (34 male, one female).

Depression, fatigue, quality of life, and subjective cognitive impairment

The results are illustrated in Table 1. Fatigue significantly improved at follow-up compared to baseline. The same held true for the psychic sum scale of the SF 12. BDI-FS scores and physical scores of the SF-12 did not change significantly. Sixty-eight percent (68.2%, $n = 15$) of the patients reported subjective cognitive complaints at baseline. At follow-up, this portion decreased to 36.4% ($n = 8$).

Neuropsychological testing

The baseline comparison for conventional neuropsychological testing was already reported in detail elsewhere (Kleefeld et al. 2017). Our patient group showed a significantly poorer performance compared to the healthy control group in the domains of visual memory/learning, attention/working memory, processing speed, executive functions, and motor skills (all $p \leq .012$). Twelve of the HCV-infected patients (54.5%) met the criteria for cognitive impairment (≥ 1 SD below mean in ≥ 2 domains) according to Antinori et al. (2007).

Longitudinal analysis revealed significant improvement (see Table 2) in the domains of visual memory/learning, executive functions, verbal fluency, processing speed, and motor skills but no improvements in the domains of learning and recall/verbal memory and attention/working memory.

After therapy, the performance of the patient group did no longer differ significantly from the control group's baseline performance in the domains of visual memory/learning (ROCF), executive functions (Color-Word-Interference Test, Trail Making Test B), and processing speed (Trail Making Test A). Although improvements were evident, patients still scored lower than controls in the domain of motor skills (Grooved Pegboard Test). The patients' individual performance trajectories for selected tests are visualized in Fig. 2. After therapy, prevalence for cognitive impairment in the patient group was reduced from 54.5 to 27.3% (12 vs. 6 patients). Patient-reported FSS, BDI-FS, and SF-12 levels did not correlate with the raw scores in any of the assessed neuropsychological domains (data not reported).

Subgroup analyses and comparisons between HCV monoinfected and HCV/HIV coinfected patients did not show significant differences in the effects of therapy on cognitive performance (all domains $p > .05$), see Suppl. Table 1.

TVA-based testing

The TVA patient subgroup did not differ significantly from the complete patient group with respect to age, gender, intelligence, and laboratory data (data not shown). The demographic data of the TVA patient sub- and their corresponding control group are shown in Table 3.

The scores predicted by the TVA modeling procedure accounted for 92.6% of the variance of the observed mean scores in the patient group at baseline and for 93.3% at follow-up, in the control group for 90.7% (baseline) and 90.8% (follow-up).

Baseline TVA parameters are illustrated in Table 3. At baseline, the patient group performed better concerning the whole

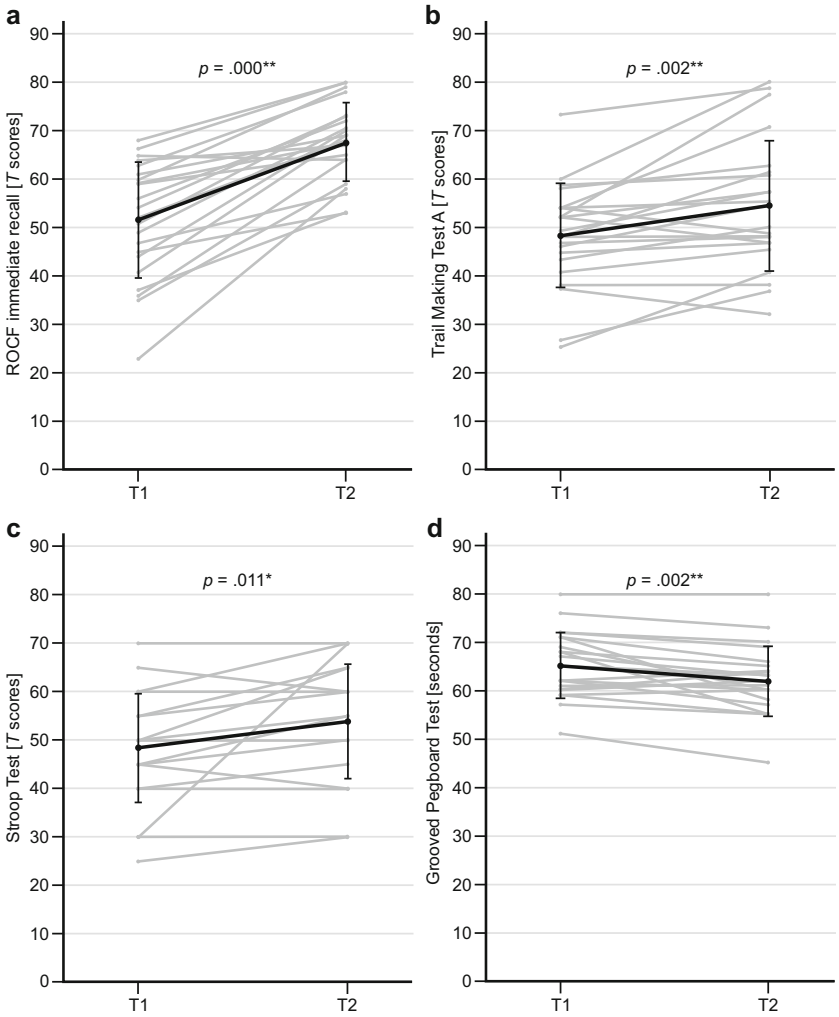

Fig. 2 Neuropsychological test battery results. The patients' individual performance trajectories of selected tests (thin grey lines), superimposed mean, and standard deviation bars (thick black lines). **a** ROCF (Rey/Osterrieth Complex Figure Test). **b** Trail Making Test Part A. **c** Color-Word-Interference Test (Stroop). **d** Grooved Pegboard Test. T1 = baseline, T2 = follow-up. *Significant at the $p < .05$ level. **Significant at the $p < .01$ level

report parameters K and C, but worse concerning t_0 and the partial report parameter α, in comparison to the control group. None of the observed differences between groups was statistically significant. On the individual level,40% ($n = 8$) of the patients were classified impaired at baseline, including the parameters K, C, t_0, and α. Considering the individual parameters, the most affected parameter was α with 25% of the patients being impaired ($n = 5$), followed by C with 15% ($n = 3$) and

Table 3 Demographic characteristics and baseline TVA parameters of the TVA patient subgroup (HCV monoinfected and HCV/HIV coinfected patients) and the TVA control group

	TVA patient subgroup ($n = 20$)	TVA control group ($n = 35$)	Test statistic and p value
Age (years)	41.95 (11.45)	45.49 (11.13)	$t(53) = 1.122$, $p = .267$
Education (years)	15.25 (2.40)	15.26 (2.32)	$t(53) = 0.011$, $p = .991$
IQ[a]	110.75 (13.73)	112.8 (13.13)	$t(53) = 0.548$, $p = .586$
K (number of letters)	3.28 (0.78)	2.99 (0.77)	$t(53) = -1.365$, $p = .178$
C (letters per second)	59.35 (36.92)	48.14 (17.87)	$t(24{,}183)^b = -1.275$, $p = .214$
t_0 (ms)	16.33 (7.41)	13.61 (8.68)	$t(53) = -1.173$, $p = .246$
α	0.92 (0.42)	0.81 (0.33)	$t(53) = -1.016$, $p = .314$
w_{index}	0.49 (0.09)	0.49 (0.10)	$t(53) = 0.110$, $p = .913$

Values are presented as mean (SD)

[a] Measured by Horn's Performance Test System (LPS), subtest 3 (Horn 1983)

[b] Degrees of freedom corrected for unequal variances

K and t_0 with 10% ($n = 2$), respectively. As the individual analysis of w_{index} revealed no distinct pattern of a visual bias to the right or left hemifield (almost equal number of patients biased to either side), this parameter was not included in the abovementioned percentage of patients classified impaired in TVA parameters. w_{index} did not differ significantly from the neutral value 0.5 in both the patient and the control group at baseline and follow-up (*t* tests for one sample, control group [baseline: mean $w_{index} = 0.49$ (SD = 0.10), $t(34) = -0.454$, $p = .653$; follow-up: mean $w_{index} = 0.49$ (SD = 0.08), $t(34) = -0.536$, $p = .595$]; patient group [baseline: mean $w_{index} = 0.49$ (SD = 0.09), $t(19) = -0.512$, $p = .614$; follow-up: mean $w_{index} = 0.49$ (SD = 0.09), $t(19) = -0.688$, $p = .500$].

At follow-up, the patient group improved their performance concerning *K*, *C*, α, and t_0, whereas the control group improved in *C* and t_0, but remained stable in *K* and α. The pre-post mixed-measure ANOVAs showed a significant main effect of time on parameter *C*, $F(1, 53) = 6.519$, $p = .014$, but no significant group effect or group × time interaction effect. Time had no significant effect on the parameters *K*, t_0, and α and w_{index}. Likewise, for these parameters, no significant group or group × time interaction effects were observed. These results are illustrated in Fig. 3. Separate pre-post performance comparisons within patient and control group, respectively, revealed no significant improvement in either the patient or the control group with exception of parameter *C* that significantly improved in the control group ($t(34) = -2.474$, $p = .018$). At follow-up, the percentage of patients classified impaired in TVA parameters was 45% ($n = 9$). The longitudinal analysis of TVA data is shown in Table 4.

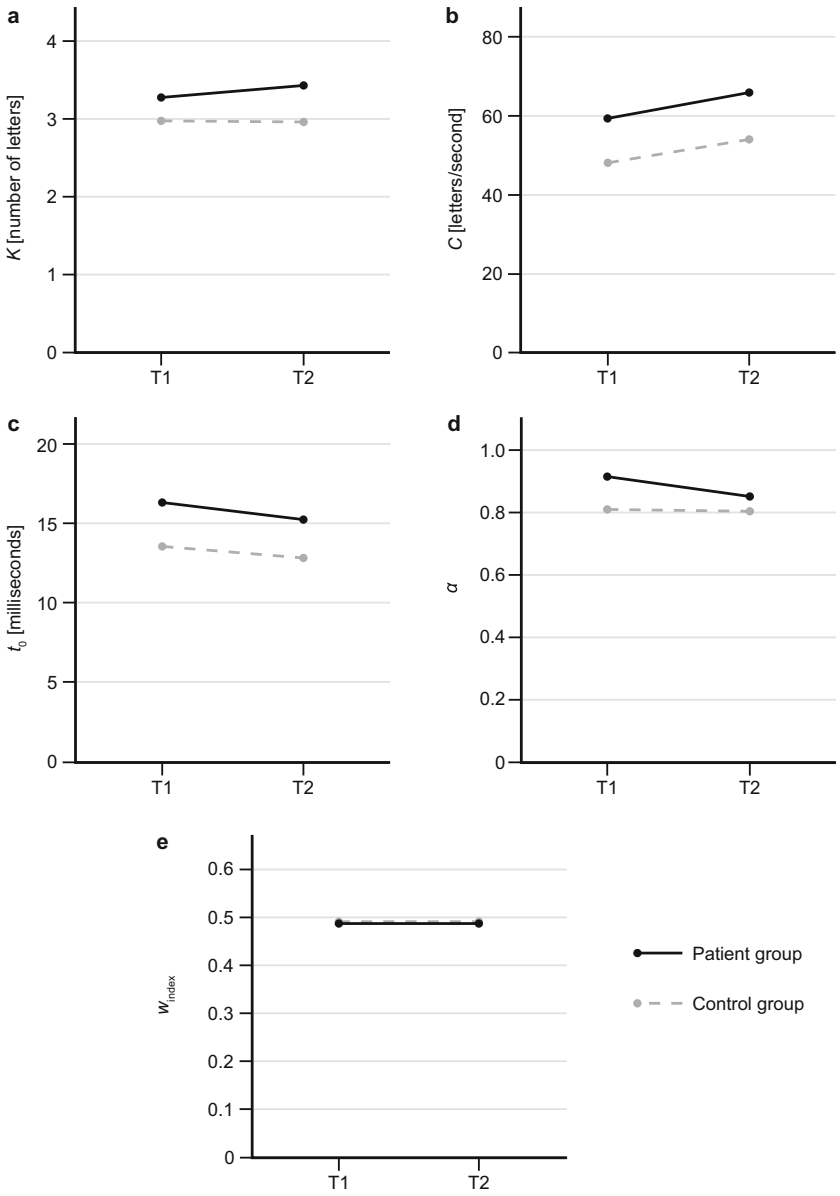

Fig. 3 TVA parameters. Mean performance of the patient group and the control group from baseline to follow-up for each TVA parameter. **a** *K* (capacity of visual short-term memory). **b** *C* (visual processing speed). **c** t_0 (perceptual threshold). **d** α (top-down controlled selectivity). **e** w_{index} (spatial distribution of attentional weighting). T1 = baseline, T2 = follow-up

Table 4 Longitudinal TVA parameter analysis of the TVA patient subgroup (HCV monoinfected and HCV/HIV coinfected patients) and the TVA control group

	TVA patient subgroup BL ($n = 20$)	TVA patient subgroup FU ($n = 20$)	Test statistic, p value	TVA control group BL ($n = 35$)	TVA control group FU ($n = 35$)	Test statistic, p value	Main effect of time	Main effect of group	Group × time interaction
K	3.28 (0.78)	3.44 (0.79)	$t(19) = -1.540$, $p = .140$	2.99 (0.77)	2.96 (0.70)	$t(34) = 0.260$, $p = .797$	$F(1, 53) = 0.928$, $p = .340$	$F(1, 53) = 3.674$, $p = .061$	$F(1, 53) = 1.664$, $p = .203$
C	59.35 (36.92)	65.87 (43.47)	$t(19) = -1.324$, $p = .201$	48.14 (17.87)	54.13 (20.34)	$t(34) = -2.474$, $p = .018$*	$F(1, 53) = 6.519$, $p = .014$*	$F(1, 53) = 2.260$, $p = .139$	$F(1, 53) = 0.012$, $p = .914$
t_0	16.33 (7.41)	15.28 (8.25)	$t(19) = 0.665$, $p = .514$	13.61 (8.68)	12.88 (9.45)	$t(34) = 0.528$, $p = .601$	$F(1, 53) = 0.660$, $p = .420$	$F(1, 53) = 1.400$, $p = .242$	$F(1, 53) = 0.020$, $p = .888$
α	0.92 (0.42)	0.85 (0.45)	$t(19) = 0.658$, $p = .518$	0.81 (0.33)	0.81 (0.39)	$t(34) = 0.117$, $p = .908$	$F(1, 53) = 0.393$, $p = .543$	$F(1, 53) = 0.664$, $p = .419$	$F(1, 53) = 0.241$, $p = .625$
w_{index}	0.49 (0.09)	0.49 (0.09)	$t(19) = 0.148$, $p = .884$	0.49 (0.10)	0.49 (0.08)	$t(34) = -0.008$, $p = .994$	$F(1, 53) = 0.014$, $p = .906$	$F(1, 53) = 0.032$, $p = .860$	$F(1, 53) = 0.016$, $p = .899$

Values are presented as mean (SD)

BL baseline, *FU* follow-up

*Significant at the $p < .05$ level

Subgroup analyses comparing monoinfected and coinfected patients revealed no significant time, infection status, or interaction effects. Separate pre-post comparisons within the monoinfected and the coinfected patient group, respectively, showed no significant performance changes (see Suppl. Table 2).

The results concerning the partial report parameters α and w_{index} did not change when excluding the patient with deuteranomaly.

Discussion

We examined cognitive functions, distinct visual attention parameters, and patient-related outcome measures for fatigue, mental health, and depression in a group of 22 HCV monoinfected and HCV/HIV coinfected patients before and after an interferon-free treatment. We expected to see significant improvements after therapy in both conventional neuropsychological testing and visual attention parameters.

Before treatment, more than half of the patients met the criteria for cognitive impairment. After HCV therapy, we observed significant improvement in fatigue and mental health as well as in five cognitive domains assessed by standardized neuropsychological testing. We did not observe significant differences in performance changes between HCV monoinfected and HCV/HIV coinfected patients. Concerning visual attention, the patients did not differ significantly from the performance change of the control group, and the portion of patients who were classified impaired in TVA parameters hardly changed from baseline to follow-up. Therefore, our hypothesis formulated at the beginning could be confirmed only in part.

Reviewing the literature, the findings on the influence of a HCV eradication on neuropsychiatric symptoms are inconclusive. Some authors showed an improved cognitive function after HCV eradication (Byrnes et al. 2012; Kraus et al. 2013). The results of a recently published study indicated that patients with SVR 12 and an increased white matter integrity showed improvements in cognition (Kuhn et al. 2017). However, patients with SVR 12, but without changes in white matter integrity, did not show significant changes in cognitive performance. In other studies, the relationship between neuropsychiatric symptoms or cognitive deficits and SVR remained unclear as they persisted after HCV eradication in HCV monoinfected patients (Pattullo et al. 2011). One study reported a decrease of fatigue levels and depression after HCV eradication, but no change in cognitive performance following interferon therapy (Huckans et al. 2015). The mentioned studies only included HCV monoinfected patients. Findings on cognitive changes after HCV eradication in HCV/HIV coinfected patients in the literature are rare. One study treating this subject found improvements in some measures of cognitive function and health-related quality of life associated with HCV clearance, HCV monoinfected and HCV/HIV coinfected patients performing similarly (Thein et al. 2007). In contrast, Marcellin et al. (2016) found persisting fatigue in the majority of a group of HCV/HIV coinfected patients after HCV therapy, not differing between the patients who cleared the virus and non-responders to therapy.

Importantly, interferon treatment has been shown to induce persistent cognitive decline (Cattie et al. 2014). For this reason, interferon treatment itself might be an important confounding factor in many studies conducted on cognitive deficits in interferon-treated HCV-infected patients.

Earlier studies also included patients with confounding factors such as liver fibrosis/cirrhosis or ongoing substance abuse (Kraus et al. 2013), which are frequent comorbidities in patients with HCV infection. By applying strict inclusion

criteria, we reduced a large HCV infected cohort to a small, but carefully selected group of patients not exhibiting the mentioned risk factors. To our knowledge, the impact of DAA treatment on cognitive functions has not been examined before. With this study, we targeted this issue for the first time based on an interferon-free HCV eradication.

All patients underwent a comprehensive, well-established battery of neuropsychological tests. The observed significant improvements in several cognitive domains and the reduction of the cognitive impairment rate at follow-up indicate a deleterious effect of HCV on the CNS that may be reversible with DAA treatment. Besides, consistent with recent literature (Gerber et al. 2016; Younossi et al. 2014), we could confirm improved patient-reported outcomes after interferon-free HCV treatment.

However, conventional neuropsychological testing did not reveal significant improvements in the domains of attention/working memory and verbal memory. A possible explanation for these findings may be the fact that we chose a relatively short retest interval of 12 weeks after therapy completion. We chose this interval, because it has been demonstrated that cerebral metabolism alterations in HCV patients were reversible within 12 weeks after successful therapy (Byrnes et al. 2012). Yet, it is possible that CNS alterations and cognitive deficits seen in HCV-positive patients may in fact take longer to improve or even persist. A recent study suggested that attention and memory deficits may persist even after successful eradication of HCV (Dirks et al. 2017). In fact, a CNS compartmentalization of the virus might represent a potential source of relapse or reactivation of the virus in cured patients and could explain the persistence of specific cognitive deficits and fatigue after HCV eradication (Tillmann 2014).

We aimed to complement the conventional neuropsychological approach by including a computer-based assessment of visual attention based on TVA for a subgroup of patients in our study. Unlike most other tests of attention, TVA-based testing does not measure reaction times but relies on accuracy-based measures and is grounded on a strong theoretical and computational background. Its strength is the representation of the real efficiency of the visual attention system, unaffected by motor processes. As HCV patients might also suffer from psychomotor impairment (von Giesen et al. 2004), the distinction between pure attentional deficits and impaired reaction times resulting from motor impairment is of importance. To minimize practice effects, a well-matched TVA control group was tested twice in a time interval comparable to that of the patients.

Although 40% of the patients were impaired in at least one TVA parameter, the baseline comparisons of TVA parameters between patients and control group were not statistically significant, indicating that our patient group did not exhibit widespread visual attentional deficits. Measured with a method independent from reaction times, visual attention deficits might be rather mild in HCV monoinfected and HCV/HIV coinfected patients. The lacking visual attention differences between the patient and the control group at baseline might have been one reason for their similar, not significantly different performance changes at follow-up. However, the portion of patients who were impaired in at least one TVA parameter did not change. The evaluation of the patient's individual follow-up performance was based on the follow-up results of the control group and therefore adequately controlled for practice effects.

We observed a significant time effect concerning parameter *C* (visual processing speed) in the mixed-measure ANOVA, which can be interpreted as a general practice effect. Although there was no significant group effect, we observed a significant improvement in parameter *C* within the control group, but not in the patient group, when considering the pre-post performance of the groups separately. TVA parameters can be susceptible to practice effects when retesting the same participants (Habekost et al. 2014). Although these observations have been made within very short retest intervals of 1 week, it might be possible that practice effects still occur after several months. A lacking practice effect in the patient group as well as the unchanged percentage of patients who were impaired in TVA parameters at follow-up after an interferon-free therapy are important observations in view of the possibility that HCV might persist in the CNS despite viral clearance from the blood.

Our study has some limitations, which should be noted. Firstly, the sample size of our patient group was small. It might be due to small group sizes that some analyses were not sufficiently powered to detect performance change differences between the patient and the control group. Concerning the analyses between HCV monoinfected and HCV/HIV coinfected patients, the lacking differences in performance changes between the two patient groups are consistent with the study of Thein et al. (2007) who suggested that both patient groups may have a similar experience in the context of HCV therapy. However, our subgroup analyses for the detection of differences in treatment effects between mono- and coinfected patients might have been limited by very small subgroup sizes.

Because almost all patients reached an SVR 12, it was not possible to compare cognitive changes between responders and non-responders to DAA therapy. As the results did not change when excluding the patient who did not reach an SVR12 (except for one small change: concerning the d2 test of attention, the *p* value changed from almost significant to marginally significant; we did not consider this as statistically robust, data not reported), we decided to keep the patient in the analysis. Therefore, it is not possible to differentiate if the observed cognitive improvements result from HCV eradication or DAA therapy.

The response rates of a DAA-based therapy often exceed 90% (Afdhal et al. 2014). For the comparison of patients who

reach SVR with a sufficiently sized group of non-responders to DAA therapy, large patient samples will be needed in the future.

Compared to the population of HCV infected patients in general, we studied a small and special subgroup of patients. Most of our patients were coinfected with HIV and acquired the HCV infection through MSM, which is not the main route of HCV transmission in general. By excluding patients with psychiatric disorders like major depression, we tried to minimize confounding factors on cognition on the one hand. On the other hand, this approach might have resulted in reduced generalizability of the results. A larger and more representative cohort of patients may have profited even more from DAA therapy. To address these issues, further studies with larger populations need to be performed.

Furthermore, an important limitation with respect to the conducted conventional neuropsychological testing are practice effects due to the lack of a twice tested control group. We aimed to minimize these effects by using parallel versions of tests for follow-up testing, and, in addition, we calculated effect sizes of changes in cognitive performance and compared these to published effect sizes of practice-related changes (see in detail Kleefeld et al. (2017)). Nevertheless, concerning the conventional test battery, practice effects might partly explain the changes in cognitive performance seen at follow-up testing and need to be mentioned as a limitation to the interpretation of our results.

Fatigue is another important aspect that should be taken into account when interpreting neuropsychological test results (Majer et al. 2008). As we saw a small, but significant improvement in self-reported fatigue levels, one could assume that decreased fatigue levels might explain the observed changes in cognitive performance. However, we did not find significant correlations between neuropsychological test results and fatigue, depression, or self-reported quality of life in our patient cohort. This might also be attributed to the small sample size. Larger sample sizes are needed to reliably assess the correlation between fatigue and cognitive performance.

The question of whether persistent cognitive impairment or absence of improvement is caused by central inflammatory processes due to persistent CNS virus invasion cannot be answered in this study. To relate clinical findings like cognitive deficits to biological changes, a combination of our methods with CSF analysis and functional imaging will be necessary in future studies, but this was beyond the scope of our work.

We evaluated cognitive performance in a cohort of HCV monoinfected and HCV/HIV coinfected patients before and after an interferon-free HCV therapy. In conclusion, our findings indicate that the DAA treatment leads to an improvement in several cognitive domains measured by standard neuropsychological testing, as well as in fatigue and mental health in both HCV monoinfected and HCV/HIV coinfected patients. Specific visual attention parameters measured by an experimental method remained relatively unaffected by HCV eradication. Persistent CNS alterations or even viral CNS persistence and a short retest interval may explain this finding. In summary, our results indicate a further advantage of DAA therapies compared to former interferon-based treatment. When planning a DAA therapy, the consideration of neuropsychological impairment could become an important aspect for practitioners. Further studies are needed to clarify whether cognitive deficits in non-cirrhotic HCV-infected patients may even represent a new indication for DAA treatment.

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Patrick Ingiliz, study concept and design, patient recruiting, revision of manuscript

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Anders Petersen, analysis and interpretation of data, revision of the manuscript

Ute Kopp, study concept and design, revision of the manuscript

Antje Kraft, study concept and design, analysis and interpretation of data, critical revision of manuscript for intellectual content

Katrin Hahn, study concept and design, interpretation of data, study supervision, critical revision of manuscript for intellectual content

Compliance with ethical standards

The study followed the ethical principles of the World Medical Association (Declaration of Helsinki) and was approved by the local ethical research committee (reference number: EA1/153/14).

Conflict of interest Felix Kleefeld reports no conflict of interest.

Sophie Heller reports no conflict of interest.

Patrick Ingiliz has received lecture or consultancy fees from AbbVie, BMS, Gilead, Janssen, and MSD.

Heiko Jessen has received payment for study cost from Gilead Sciences GmbH; for Board membership from Gilead Sciences GmbH, Bioscientia-Institut für Medizinische Diagnostik GmbH, and ViiV Healthcare GmbH; for speaker activities from ViiV Healthcare GmbH, AbbVie Deutschland GmbH & Co. KG, Bristol-Myers Squib GmbH & Co KGaA, Gilead Sciences GmbH, Gilead Sciences Ltd.; and for travel/accommodation/meeting expenses from ViiV Healthcare GmbH, AbbVie Deutschland GmbH & Co. KG, Bristol-Myers Squib GmbH & Co KGaA, Gilead Sciences GmbH, Gilead Sciences Ltd.

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