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Neuropsychiatric and laboratory outcomes of hepatitis C treatment in an early-treated HIV cohort in Thailand

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Abstract

Background Hepatitis C virus (HCV) coinfection may further compromise immunological and cognitive function in people with HIV (PWH). This study compared laboratory and neuropsychiatric measures across the periods of HCV seroconversion and direct-acting antiviral (DAA) therapy with sustained virologic response (SVR) among PWH who initiated antiretroviral therapy (ART) during acute HIV infection (AHI) and acquired HCV after 24 weeks of ART.

Methods Participants from the RV254 AHI cohort underwent paired laboratory and neuropsychiatric assessments during follow-up visits. The former included measurements of CD4+and CD8+T-cell counts, HIV RNA, liver enzymes, and lipid profiles. The latter included the Patient Health Questionnaire-9 (PHQ-9), Distress Thermometer (DT), and a 4-test cognitive battery that evaluated psychomotor speed, executive function, fine motor speed, and dexterity. The raw scores in the battery were standardized and averaged to create an aggregate performance (NPZ-4) score. Parameters of HCV-coinfected participants were compared across the periods of HCV seroconversion and DAA treatment.

Results Between 2009 and 2022, 79 of 703 RV254 participants acquired HCV after ≥ 24 weeks of ART; 53 received DAA, and 50 (94%) achieved SVR. All participants were Thai males (median age: 30 years); 34 (68%) denied past intravenous drug use, and 41 (82%) had a history of other sexually transmitted infections during follow-up. Following SVR, aspartate transferase (AST) and alanine transaminase (ALT) decreased ($p < 0.001$), while total cholesterol, low-density lipoprotein, and triglycerides increased ($p < 0.01$). The median CD4+/CD8+ratio increased from 0.91 to 0.97 ($p = 0.012$). NPZ-4 improved from 0.75 to 0.91 ($p = 0.004$). The median DT score increased from 1.7 to 2.7 ($p = 0.045$), but the PHQ-9 score remained unchanged.

Conclusion HCV coinfection is common in this group of high-risk PWH, highlighting the need for regular screening, early diagnosis, and treatment. The study participants exhibited a modest improvement in the CD4+/CD8+T-cell ratio and cognitive performance following DAA therapy and SVR. Future studies should examine potential neuropsychiatric impacts during early HCV infection as well as the longer-term neuropsychiatric outcomes after DAA treatment with SVR.

Keywords HIV, Hepatitis C, HIV/HCV coinfection, Direct-acting antivirals, SVR, Cognitive, PWH

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Background

HIV and Hepatitis C virus (HCV) share common modes of transmission, including sexual contact, needle-sharing during intravenous drug use (IVDU), and blood product transfusion [1]. In people with HIV (PWH), the prevalence of HCV coinfection is 6.4% in men who have sex with men (MSM) [1]. Furthermore, PWH have a sixfold higher risk of HCV infection than people without HIV (PWoH) [1]. Compared to HIV monoinfection and HCV monoinfection, HIV/HCV coinfection is linked with higher risks of death, liver failure, and extrahepatic manifestations, including cognitive and affective disorders [2–5], indicating that disease progression is accelerated in individuals with dual infections.

Compared to older forms of HCV treatment, the advent of direct-acting antivirals (DAAs) has resulted in high HCV cure rates (measured as sustained virologic response, SVR) with more favorable safety profiles [6]. DAAs inhibit the nonstructural proteins that are responsible for viral replication [7]. Remarkably, DAAs are effective regardless of age, sex, prior HCV treatment outcomes, or degree of liver fibrosis [8]. Improvements in HCV-related extrahepatic symptoms following DAA therapy and SVR were observed in HCV-monoinfected [9] as well as HIV/HCV-coinfected individuals [10].

To date, the majority of studies that evaluated the impact of HCV treatment on immunologic and neuropsychiatric outcomes have been conducted on PWH who initiated ART during chronic HIV infection, with varied HIV suppression status, and frequently with an uncertain duration of HCV infection [6, 8]. Moreover, only a few of them provided a simultaneous account of changes before and after HCV seroconversion, prior to HCV treatment. This study examined the changes in laboratory and neuropsychiatric parameters during the periods of HCV seroconversion and DAA therapy with SVR among research participants from a Thai acute HIV infection (AHI) cohort who were on antiretroviral therapy (ART).

Methods

Study design and participants

The study participants were from the RV254 AHI cohort study in Bangkok, Thailand, which enrolled individuals with Fiebig stages I-V AHI [11]. RV254 participants commenced ART within a median of 3 days post-enrollment and were longitudinally followed. They were screened for HCV infection every 48 weeks using an HCV-antibody test, and active infection was confirmed through HCV RNA measurement via the Xpert HCV Assay (Cepheid, Sunnyvale, CA). The study protocol was approved by the institutional review boards of all relevant collaborating institutions. All participants provided written informed consent.

Participant selection

The analysis included participants who met the following criteria: (1) tested negative for HCV antibody at enrollment; (2) had ≥ 24 weeks of ART with suppressed HIV RNA levels (< 50 copies/ml) before initiating DAA treatment; (3) achieved SVR with undetectable HCV RNA ≥ 12 weeks following a standard course of DAA treatment; and (4) completed paired laboratory and neuropsychiatric assessments before and after DAA therapy with SVR, based on the RV254 study protocol (see below).

Laboratory and clinical investigations

Blood tests included liver enzyme (aspartate transferase (AST) and alanine transaminase (ALT)) levels, total cholesterol, low-density lipoprotein (LDL), and triglycerides, as well as HIV-related immunologic and virologic parameters (plasma HIV RNA, CD4+, and CD8+T-cell counts). Additionally, non-treponemal syphilis testing and nucleic acid amplification tests for chlamydia and gonorrhea are performed every 24 and 48 weeks, respectively. Participants are also screened for peripheral neuropathy by research physicians every 48 weeks (Supplementary Table S1).

Neuropsychiatric assessments

All RV254 participants underwent neuropsychiatric assessments at enrollment; at 12, 24, and 48 weeks; and every 48 weeks thereafter. Mood assessments included the Patient Health Questionnaire-9 (PHQ-9) and the Distress Thermometer (DT). Both have been validated for use in Thailand [12–14]. The PHQ-9 is a 9-item measure of depressive symptoms (score range 0–27) based on the DSM-IV [15]. Total scores of ≥ 10 and ≥ 15 indicate moderate and moderate-severe depression, respectively [15]. The DT is a self-reported measure of emotional distress, similar to a visual analog scale, with a range from 0 to 10 [16].

Cognitive assessment was based on a four-test battery that measured motor speed and dexterity (nondominant hand Grooved Pegboard test; Lafayette Instrument Company, Lafayette, IN, USA), psychomotor speed (Color Trails 1 and Trail Making Test A; PAR, Inc., Lutz, FL, USA), and executive functioning (Color Trails 2; PAR, Inc., Lutz, FL, USA). The raw scores for each test were standardized to z-scores using Thai normative data [17], and averaged to obtain an aggregate performance (NPZ-4) score. Individual as well as aggregate test performances were included in the analyses.

Data analysis

The paired laboratory and neuropsychiatric measures of the participants with HCV were assessed across two separate periods, specifically in relation to HCV seroconversion and DAA therapy: (1) ***Pre-HCV seroconversion***: last visit before HCV seroconversion versus ***Post-HCV seroconversion***: first visit after HCV seroconversion; and (2) ***Pre-DAA***: last visit before DAA initiation versus ***Post-DAA***: first visit after completion of DAA therapy with SVR. Outcomes are reported as medians (interquartile ranges, IQRs) or frequencies (percentages) and were analyzed using McNemar's test and the Wilcoxon signed-rank test in StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.

Results

Between May 2009 and July 2022, 109 (15.5%) out of 703 RV254 participants were diagnosed with HCV: 16 tested positive for anti-HCV antibody at enrollment (week 0), 12 seroconverted between weeks 1 and 24, and 79 were diagnosed after 24 weeks of ART; 2 withdrew from the study at the time of analysis. Among the 79 participants who seroconverted after 24 weeks of ART, 53 completed DAA therapy with HCV RNA level measurements at least 3 months after DAA therapy. Of these, 50 (94%) achieved SVR and were included in the current analysis (Fig. 1).

All 50 participants were Thai males with a median age of 30 [IQR 26–35] years. The median duration from RV254 enrollment to HCV seroconversion was 192 [IQR 96–318] weeks. Forty-three (86%) were infected with HCV genotype 1. Thirty-four (68%) denied any

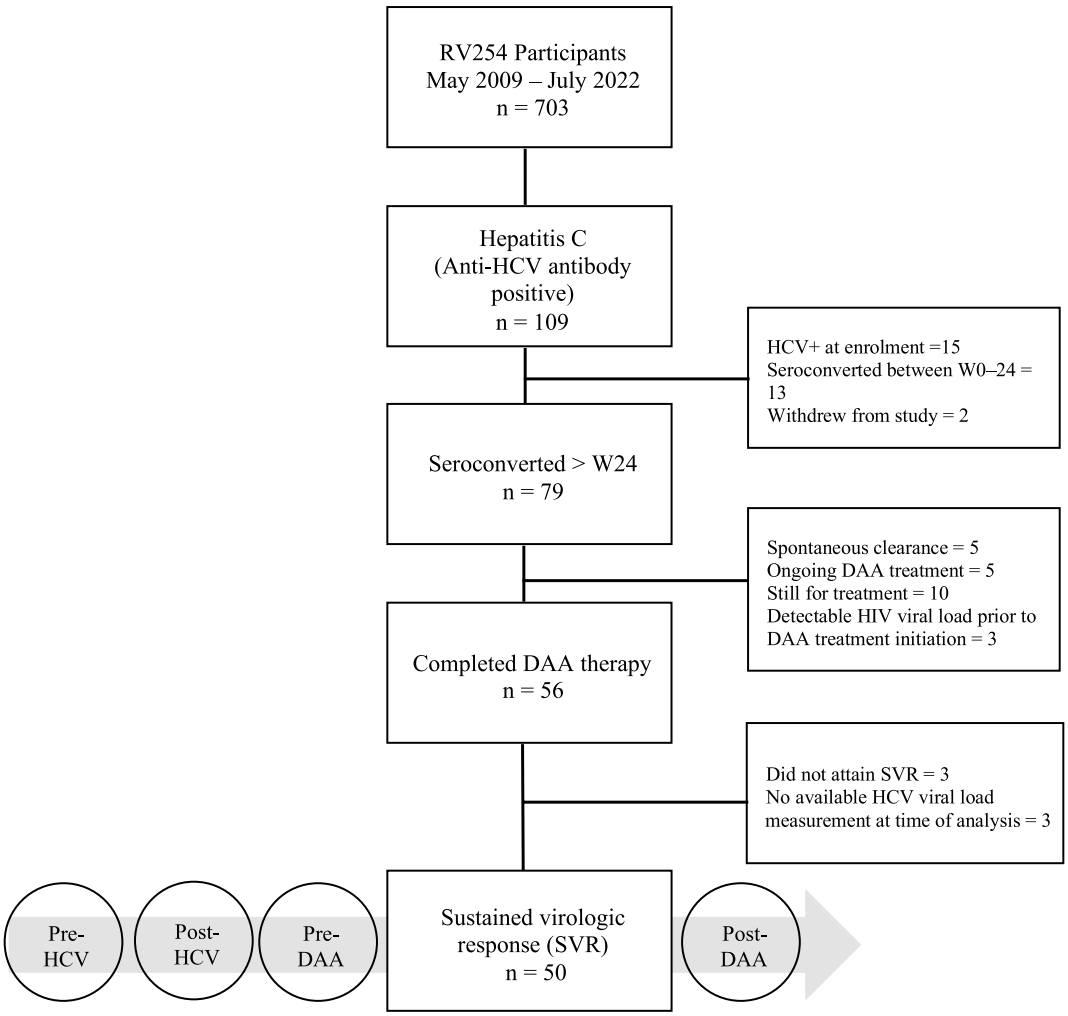

Fig. 1 Study participant identification and selection

prior IVDU, while 41 (82%) contracted other sexually transmitted infections (STIs), including syphilis, gonorrhea, and chlamydia, during follow-up (Table 1). The median durations between HCV seroconversion and pre-DAA assessment and between DAA completion and post-DAA assessment were 15 [IQR 9, 29] and 27 [IQR 20–38] weeks, respectively. The predominant DAA regimens used were sofosbuvir/ledipasvir (52%) and sofosbuvir/velpatasvir (36%). None reported DAA-related adverse events.

Table 1 Participants' characteristics[a] (N = 50)

Age, years	**30 (26, 35)**
Male sex, n (%)	50 (100)
Weight, kg	62.8 (54.9, 71.4)
Body mass index, kg/m^2	21.4 (19.08, 24.1)
Duration from acute HIV to HCV seroconversion, weeks	192 (96, 318)
Plasma HIV RNA at HCV seroconversion, log10 cps/ml	1.3 (1.3, 1.3)
Plasma HCV RNA at HCV seroconversion, log10 cps/ml	5.90 (4.84, 6.76)
HCV Genotype, n (%)	
1	43 (86)
3	2 (4)
Not determined	5 (10)
Sexual Orientation, n (%)	
MSM	
Homosexual	47 (94)
Bisexual	3 (6)
Heterosexual	0 (0)
Substance use, n (%)	
Intravenous	16 (32)
Oral/Inhalational	14 (28)
Incident Sexually transmitted infection, n (%)	
Syphilis	37 (74)
Gonorrhea	41 (82)
Chlamydia	35 (70)
Hepatitis B co-infection (+ HBs antigen), n (%)	0 (0)
Transfusion products, n (%)	0 (0)
Duration between HCV diagnosis and DAA initiation, weeks	55 (29, 69)
ART Regimen prior to HCV seroconversion, n (%)	
Dolutegravir-based	44 (88)
Efavirenz-based	6 (12)
DAA Regimens, n (%)	
Sofosbuvir/Ledipasvir	26 (52)
Sofosbuvir/Velpatasvir	18 (36)
Sofosbuvir/Daclatasvir	3 (6)
Sofosbuvir/Ravidasvir	3 (6)

[a] Median (IQR) is provided unless specified

Laboratory outcomes

Table 2 compares the outcome measures across the periods of HCV seroconversion (pre-HCV seroconversion vs. post-HCV seroconversion, median duration 49 IQR [47–91] weeks) and DAA treatment (pre-DAA vs. post-DAA and SVR, median duration 49 IQR [48–68] weeks). Notably, measures of 38 participants (76%) post-HCV seroconversion and pre-DAA originated from the same follow-up visit in 38 participants (76%). The levels of ALT (28.5 IQR [18.8, 48.3] vs. 98.5 IQR [49–180]) and AST (20.5 IQR [16–25.5] vs. 56 IQR [36–100]) increased after HCV seroconversion ($p < 0.001$) and subsequently decreased (ALT: 99 IQR [49–179] vs. 19 IQR [13–26], $p < 0.001$; AST: 56 IQR [36–100] vs. 20 IQR [16–25], $p < 0.001$) following DAA and SVR. The lipid parameters were not significantly different after HCV seroconversion. However, the levels of total cholesterol (184 IQR [159–210] vs. 201 IQR [174–225]), LDL (113 IQR [94–138] vs. 136 IQR [111–160]), and triglycerides (87 IQR [72–119] vs. 112 IQR [82–161]) increased after DAA treatment in patients who achieved SVR ($p < 0.001$). The levels of hemoglobin, total white blood cell count, and platelet count remained statistically unchanged across all time points.

Following HCV seroconversion, there were significant increases in the CD4 + (639 IQR [496–768] vs. 687 IQR [569.50–815], $p = 0.03$) and CD8 + (669 IQR [550–852] vs. 776 IQR [586–912], $p = 0.03$) T-cell counts, followed by an insignificant decrease after DAA treatment with SVR. On the other hand, the median CD4 + /CD8 + T-cell ratio was not significantly different after HCV seroconversion but increased from 0.91 [IQR 0.73–1.1] to 0.97 [IQR 0.76–1.29] ($p = 0.012$) following DAA treatment and SVR. The plasma HIV suppression rate remained unchanged throughout the two periods.

Neurological and neuropsychiatric outcomes

None of the 50 participants exhibited signs of peripheral neuropathy before or immediately after seroconversion, but two (4%) demonstrated signs of peripheral neuropathy prior to the initiation of DAA treatment. One participant (2%) demonstrated persistent signs of peripheral neuropathy after DAA therapy with SVR. Cognitive test performance, including the composite NPZ-4 and z-scores in each of the 4 tests, was statistically unchanged after HCV seroconversion. Following DAA treatment and SVR, NPZ-4 modestly improved from 0.75 [IQR 0.42–1.02] to 0.91 [IQR 0.55–1.31] ($p = 0.004$). The change was accompanied by an improvement in the median z-scores of all four cognitive tests. However, only the improvement in the Trail Making A test score was statistically significant (0.60 [IQR 0.17–1.32] vs. 0.91

Table 2 Laboratory and clinical outcomes across HCV seroconversion and DAA treatment with SVR

Parameters	Pre-HCV Seroconversion[a]	Post-HCV Seroconversion[b]	p- value	Pre-DAA[c]	Post-DAA[d]	p- value
Biochemistry and Hematologic						
ALT, U/L	28.5 (18.8, 48.3)	98.5 (49,180)	**< 0.001**	99 (49, 179)	19 (13, 26)	**< 0.001**
AST[e], U/L	20.5 (16, 25.5)	56 (36, 100)	**< 0.001**	56 (36, 100)	20 (16, 25)	**< 0.001**
Plasma HCV RNA, log10 cps/mL	0	6.35 (5.33, 6.91)	**< 0.001**	6.35 (5.33, 6.91)	< 1.08 (1.08, 1.08)	**< 0.001**
Total white blood cell count, 10^9/L	6.09 (5.12, 7.05)	5.99 (4.85, 6.95)	0.19	5.99 (4.86, 6.94)	5.8 (4.92, 6.88)	0.96
Platelet count, 10^9/L	265 (241, 306)	269 (245, 298)	0.95	269 (246, 298)	277 (246, 304)	0.57
Hemoglobin, g/dL	14.8 (14.3, 15.4)	15.1 (14.3, 15.5)	0.06	15.1 (14.3, 15.5)	14.9 (13.7, 15.6)	0.15
Total cholesterol, mg/dL	185 (158, 212)	184 (159, 210)	0.48	184 (159, 210)	201 (174, 225)	**< 0.001**
Low density lipoprotein (LDL), mg/dL	121 (96, 138)	113 (94, 140)	0.66	113 (94, 138)	136 (111, 160)	**< 0.001**
Triglycerides, mg/dL	86 (64, 135)	87 (72, 121)	0.53	87 (72, 119)	112 (82, 161)	**0.003**
Immunologic and Virologic						
CD4 + T-cell count, cells/mm^3	639 (496, 768)	687 (569.50, 815)	**0.03**	687 (571, 813)	660 (513, 925)	0.99
CD8 + T-cell count, cells/mm^3	669 (550, 852)	776 (586, 912)	**0.03**	776 (588, 909)	736 (542, 863)	0.17
CD4/CD8 ratio	0.90 (0.77, 1.14)	0.91 (0.73,1.10)	1.00	0.91 (0.73, 1.1)	0.97 (0.76, 1.29)	**0.012**
HIV RNA < 50 copies/ ml, n (%)	49 (98)	50 (100)	0.60	50 (100)	50 (100)	1.00
Peripheral neuropathy, n (%)	0 (0)	0 (0)	1.00	2 (4)	1 (2)	1.00
Cognitive Tests						
NPZ-4 score	0.72 (0.30, 1.15)	0.75 (0.40, 1.02)	0.65	0.75 (0.42, 1.02)	0.91 (0.55, 1.31)	**0.004**
z-Color Trails 1	1.30 (0.70, 1.62)	1.23 (0.70, 1.66)	0.63	1.23 (0.74, 1.65)	1.29 (0.84, 1.73)	0.29
z-Color Trails 2	0.59 (-0.10, 1.16)	0.78 (0.21, 1.48)	0.06	0.78 (0.21, 1.46)	0.92 (0.44, 1.26)	0.52
z-Grooved Pegboard	0.62 (-0.10, 1.38)	0.43 (-0.49, 1.22)	0.10	0.43 (-0.49, 1.19)	0.79 (-0.05, 1.38)	0.08
z-Trails Making A	0.85 (0.15, 1.19)	0.60 (0.13, 1.33)	0.18	0.60 (0.17, 1.32)	0.91 (0.4, 1.4)	**0.03**
Mood Assessments						
PHQ-9 total score (range 0–27)	6 (2,9)	6 (2, 8)	0.58	6 (2, 8)	4 (2, 8)	0.72
PHQ-9 ≥ 10, n (%)	5 (10)	7 (14)	0.38	11 (22)	9 (18)	0.73
PHQ-9 ≥ 15, n (%)	3 (6)	4 (8)	0.70	4 (8)	3 (6)	1
Distress Thermometer (range 0–10)	2 (0.9, 4.0)	1.7 (1, 4.2)	0.25	1.7 (1, 4.2)	2.7 (1.1, 5)	**0.05**

[a] Last visit prior to HCV seroconversion

[b] First visit after HCV seroconversion

[c] Last visit prior to initiation of DAA treatment; Median of 15 weeks (IQR 9—29) before DAA

[d] First visit after completion of DAA treatment and SVR; Median of 27 weeks (IQR 20—38) after DAA

[e] n = 34

[IQR 0.4–1.4], $p = 0.028$). The median DT and PHQ-9 scores remained similar before and after HCV seroconversion. After DAA therapy and SVR, the median DT score increased from 1.7 [IQR 1–4.2] to 2.7 [IQR 1.1–5] ($p = 0.045$). The PHQ-9 total score and the frequencies of moderate and moderate-severe depression remained statistically unchanged.

Discussion

We previously reported an HCV epidemic among HIV-infected men who have sex with men (MSM) in Bangkok, Thailand [18, 19]. In the current study, we observed a 16% prevalence of HCV infection in this young, MSM-predominant AHI cohort, with an 11% cumulative incidence of HCV seroconversion among participants on stable (> 24 weeks) ART. In comparison, a global systematic review reported that the prevalence of HCV coinfection in MSM with HIV is approximately 6.4% [1]. Notably, the main route of HCV transmission in our cohort was likely through sexual behavior, primarily anal sex, often in the context of substance use and group sex [18]. While 32% of the study participants reported a history of IVDU, problematic substance use and substance dependence were rare, as indicated by clinician interviews during follow-up visits.

Consistent with the high efficacy and safety profile of DAAs [7], the treatment success rate was 94%, and DAA-related adverse events were not observed in this study. The levels of liver enzymes decreased post-DAA, reflecting the resolution of HCV-related hepatic inflammation. Previous studies have demonstrated increased hemoglobin levels, total leukocyte counts, and platelet counts following DAA therapy with SVR [20–22], but these changes were not observed here. The hematological benefits described in prior studies may be attributed to improvements in liver fibrosis, portal hypertension, and anemia associated with chronic illness after SVR [23]. These hematological changes were not observed in this study, most likely because our participants are relatively young MSM who had normal hematological parameters and lacked major hepatic complications before DAA initiation. Nevertheless, we observed increases in total cholesterol, triglyceride, and LDL levels following SVR, as reported in studies with HCV-monoinfected [24–26] and HIV/HCV-coinfected participants [27]. HCV infection is associated with decreased total cholesterol and LDL levels via activation of LDL receptor expression and modulation of proteins involved in liver steatosis [27, 28]. Thus, the reversal of these processes following HCV eradication may result in paradoxical increases in serum lipid levels.

HIV-related immune and virologic parameters

HCV infection has been reported to associate with suboptimal ART response and CD4 + T-cell recovery in ART-naïve PWH [29]. HCV infection activates CD8 + T-cells and potentially inhibits their downregulation following ART and HIV suppression [30], thereby worsening CD4 + /CD8 + T-cell ratio inversion [31]. Two earlier studies reported unchanged CD4 + T-cell counts in PWH post-SVR [32, 33]. While two studies reported a decrease in the CD8 + T-cell count post-SVR [32, 34], only one reported a concomitant CD4 + /CD8 + T-cell ratio improvement [34]. In this study, the CD4 + /CD8 + T-cell ratio modestly increased without statistically significant changes in CD4 + and CD8 + T-cell counts following DAA and SVR, within the context of stable HIV suppression. Nonetheless, in the absence of a comparison group of HIV-monoinfected and HCV-monoinfected individuals, disentangling the effects of DAA treatment from those of ART on CD4 + /CD8 + T-cell recovery is challenging.

Neurological and neuropsychiatric outcomes

Neurological manifestations, such as cognitive impairment, mood disorders , and peripheral neuropathy, have been reported in both HCV-monoinfection and HIV/HCV-coinfection [35–38]. In this study, peripheral neuropathy was uncommon and was identified in 2 participants (4%) who exhibited mild impairment of distal vibration sense within six months of HCV seroconversion. The neuropathy symptoms were considered HCV-related given their temporal relationship, stable HIV suppression, and normal levels of folate, vitamin B12, and glycosylated hemoglobin (HbA1c). In one HCV-monoinfection study, neuropathy symptoms improved in half of the participants following DAA therapy [39], whereas one out of two participants in our study experienced resolved neuropathy symptoms nine months after DAA therapy.

Surprisingly, DT scores rose post-DAA in this study, in contrast to a reduction observed in a prospective study with 90 HCV-monoinfected participants [40]. Nonetheless, the median DT score post-DAA in the current study remained well below the commonly referred cutoff score (≥ 4) which signifies clinically significant distress [41]. Further, the PHQ-9 score did not indicate any worsening of depressive symptoms.

HCV infection may affect cognition [42, 43] via direct neurotoxicity, neuroinflammation, and hepatic encephalopathy [42–44]. HCV/HIV coinfection has been associated with worse cognition than either HIV or HCV monoinfection [45–47]. Most studies have found considerable cognitive improvement after DAA with SVR, especially in visual learning/memory, processing speed, motor skills, executive functions, and verbal fluency [47–49]. In our study, both the aggregate score and z-score of the Trail Making A test (a test of psychomotor speed) improved post-DAA. Notably, both indices were within the normal range before DAA, and the magnitude of improvement was modest, falling within the standard error of measurement.

To our knowledge, this is the first study to provide a longitudinal assessment of laboratory, cognitive, and mood outcomes in PWH across the periods of HCV seroconversion and DAA therapy. The analysis was based on a longitudinal cohort of PWH who initiated ART during acute HIV and acquired HCV while on stable ART for more than 24 weeks. The current study design has partially addressed several methodological confounders that are present in earlier studies on cognitive outcomes following DAA therapy and HCV eradication. First, practice effects enhance performance in several cognitive domains, particularly between the first and second test exposures [50]. The participants in the current study had completed the same cognitive battery multiple times before DAA therapy was initiated, thus passing the critical phase of practice effects and limiting the potential benefits thereof. Second, disentangling the potential cognitive benefits of HCV eradication from those of ART in PWH is challenging, as cognitive improvement related

to the latter may take weeks to months before reaching a plateau [51]. Similarly, CD4 + and CD8 + T-cell counts continue to evolve for months after ART initiation [52]. In this study, the potential immunological and cognitive benefits of ART were minimized by the sustained intake of ART for more than 2 years prior to initiation of DAA therapy in most of the participants. The initially statistically unchanged NPZ-4 and CD4 + /CD8 + scores after HCV seroconversion and the subsequent improvement in these parameters after DAA treatment with SVR raise the question of whether the observed improvement is due to DAA treatment and HCV eradication.

Limitations of this study include the sample size, short follow-up duration, male-only setting, the absence of liver elastography to grade the severity of liver disease, and the lack of HCV-monoinfected controls to determine whether the observed changes are HIV/HCV-coinfection specific.

Conclusion

Consistent with existing reports, this study highlighted the high rate of HCV coinfection among young MSM with HIV in our locality. They responded well to DAA treatment, achieving a high rate of HCV eradication. These findings indicate the necessity of incorporating routine HCV screening for early diagnosis, along with educational materials on HCV prevention, into ongoing HIV/AIDS programs. We observed modest improvements in cognitive test performance and the CD4 + / CD8 + T-cell ratio following DAA therapy and SVR but not during the period after HCV seroconversion. The discordant outcomes between the two periods may suggest an early neuropsychiatric impact of HCV infection, which was subsequently reversed by prompt initiation of HCV treatment and eradication. Future studies with HIV- and HCV-monoinfected controls should focus on the early neuropsychiatric impacts of HCV infection as well as the longer-term neuropsychiatric outcomes following DAA therapy with SVR.

Disclaimer

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, the National Institutes of Health, the Department of Health and Human Services, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. The investigators have adhered to the policies for protection of human subjects as prescribed in AR-70–25.

Abbreviations

ART	Antiretroviral therapy
DAA	Direct-acting antiviral
CT1	Color Trails 1
CT2	Color Trails 2
DT	Distress Thermometer
GPB	Grooved Pegboard
HIV	Human immunodeficiency virus (HIV)
HCV	Hepatitis C virus
IVDU	Intravenous drug use
PWH	People with HIV
STI	Sexually transmitted infection
SVR	Sustained virologic response
TMA	Trails Making A

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Author contributions

FO: Study concept and design, acquisition of data, data curation, formal analysis and interpretation of results, drafting of manuscript, review and editing CS: Study concept and design, critical revision of the manuscript for important intellectual content; SP: Statistical analysis, manuscript preparation, critical revision of the manuscript for important intellectual content MP: statistical analysis, manuscript preparation, critical revision of the manuscript for important intellectual content TW: critical revision of the manuscript for important intellectual content DH: Methodology, interpretation of results, critical revision of the manuscript for important intellectual content NP: acquisition of data SSN: critical revision of the manuscript for important intellectual content RP: critical revision of the manuscript for important intellectual content NP: critical revision of the manuscript for important intellectual content DC: critical revision of the manuscript for important intellectual content LT: critical revision of the manuscript for important intellectual content SS: Study concept and design, methodology, interpretation of results, critical revision of the manuscript for important intellectual content, study supervision PC: Study concept and design, methodology, interpretation of results, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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Data availability

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review boards of all relevant collaborating institutions. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The RV254/SEARCH 010 study participants received antiretroviral drugs from the Thai Government Pharmaceutical Organization, Gilead Science, Merck, and ViiV Healthcare. SS reports grants from the NIH–NIMH and NINDS during the study and nonfinancial support from ViiV Healthcare, Inc., in the form of

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