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Original article

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Background: Despite a rising incidence of acute HCV in patients infected with HIV, the optimal therapeutic strategy (pegylated interferon-α [PEG-IFN-α] monotherapy or in combination with ribavirin) is still under debate.
Methods: A total of 23 HIV-infected patients were prospectively diagnosed with acute HCV and treated with PEG-IFN-α2a monotherapy (180 μg/week) for 24 or 48 weeks. Add-on ribavirin was allowed from week 4 of therapy onwards. There were three patients who were not included for different reasons. Blood samples were routinely drawn for viral load measurement and IL28B polymorphism analysis.
Results: Spontaneous viral clearance occurred in 1 (4%) patient. Nineteen patients (13 genotype 1 and 6 genotype 4) received treatment with PEG-IFN-α monotherapy (3 with add-on ribavirin) resulting in a rapid virological response (HCV RNA<50 IU/ml at week 4) in 7 (37%) patients. A sustained virological response (SVR) was reached in 7 (37%) patients, whereas 9 (47%) patients were null-responders to treatment (that is, <2 $\log_{10}$ drop in HCV RNA at week 12 of therapy). The unfavourable G allele of the IL28B polymorphism rs8099917 was detected in 66% of the non-responders. In case of re-emergence of HCV viraemia after treatment discontinuation, sequence analysis of quasispecies confirmed an HCV relapse in 3 patients while 2 patients were re-infected by their previously non-responding partner.
Conclusions: PEG-IFN-α monotherapy resulted in a low SVR rate and a high percentage of null-response, whereas non-SVR was associated with a polymorphism in the IL28B gene (rs8099917).

Introduction

In recent years, the incidence of acute HCV infections among men having sex with men (MSM) infected with HIV has markedly increased [1–3]. Recent phylogenetic analysis revealed clustering of specific HCV strains among large international HIV-positive MSM networks with permucosal exposure as the most likely transmission route [1,4]. Since acute HCV in HIV-infected patients rarely presents with overt clinical symptoms, yearly testing for the presence of HCV antibodies and routine laboratory assessment of transaminases is the preferred method of screening [5]. Failure to diagnose HCV in the acute phase of the infection compromises the chances of cure as higher rates of sustained virological response (SVR) are seen upon early therapy when compared with treatment of chronic HCV [6].

In contrast to HCV-monoinfected patients, where SVR rates between 72% and 94% are reached with pegylated interferon-α (PEG-IFN-α) and IFN-α monotherapy [7–9], the optimal treatment strategy for acute HCV in HIV-infected patients is debated [10,11]. In HIV-infected patients with acute HCV fairly consistent SVR rates of approximately 51–80% have been reported with combination therapy of PEG-IFN-α and ribavirin [12–18]. However, treatment with PEG-IFN-α monotherapy has resulted in a wide variance of SVR rates from 0% to 100% [19–23]. Two prospective

non-randomized trials have compared PEG-IFN-α monotherapy with PEG-IFN-α/ribavirin combination therapy with one study [24] showing superiority of PEG-IFN-α monotherapy over combination therapy while the other study [25] reported the opposite result. Comparing these trials is difficult because of differences in study design and patient characteristics.

This is the largest prospective cohort study of HIV-infected patients with acute HCV to analyse the efficacy of PEG-IFN-α monotherapy. Since recent publications highlight the importance of IL28B gene single nucleotide polymorphism (SNP) in spontaneous clearance in acute HCV [26] and either a favourable outcome [27,28] or non-response [29,30] to PEG-IFN-α/ribavirin therapy in chronic HCV genotype 1 infections, this study evaluated the role of IL28B SNP in treatment outcome of PEG-IFN-α monotherapy in HIV-infected patients with acute HCV.

Methods

Patient cohort

All HIV patients in follow-up in two academic hospitals (University Medical Center Utrecht [UMCU; Utrecht, the Netherlands] and University Medical Center Groningen [UMCG; Groningen, the Netherlands]) consecutively being diagnosed with acute HCV infection between January 2006 and January 2009, were included in this study. Routine monitoring of liver enzymes every 3 to 4 months and yearly screening for HCV antibodies was performed in all patients. Diagnosis of acute HCV was based on the presence of all three criteria: detectable plasma HCV RNA (COBAS TaqMan 2.0 [Roche Molecular Diagnostics, Almere, the Netherlands] or real-time PCR [Abbott Diagnostics, Hoofddorp, the Netherlands]), anti-HCV seroconversion (AxSYM automated immunoassay instrument system or Abbott Architect CMIA 3.0 [Abbott Diagnostics]) following any elevation of liver enzymes above the upper limit of normal (ULN; ULN=35 U/l) compared with previous measurements, and negative HCV serology in the last stored plasma samples within the previous 6 (n=18) to 12 months (n=5) before diagnosis. HCV genotype was determined by second-generation InnoLIPA assay (Versant HCV genotype 2.0 assay; Siemens Healthcare Diagnostics, Breda, the Netherlands).

Treatment

Patients were treated and followed up by their own physicians in accordance with international guidelines [6,31]. After the diagnosis of acute HCV, spontaneous viral clearance was awaited for 12 weeks after which anti-HCV treatment was initiated with PEG-IFN-α2a 180 μg/week (Pegasys®; Roche, Basel, Switzerland). When no rapid virological response (RVR; that is, HCV RNA<50 IU/ml) but >2 $\log_{10}$ decrease in HCV RNA was observed at week 4 of therapy, addition of weight-based ribavirin (<75 kg: 1,000 mg in two daily doses; ≥75 kg: 1,200 mg in two daily doses; Copegus®; Roche) was allowed. Patients were treated 24 or 48 weeks at the discretion of the treating physician. A 12-week on-treatment analysis showing high rates of non-response [32], resulted in modification of our treatment practice and thereby ending the inclusion of patients into this cohort.

Viral load and definitions

Plasma HCV RNA was routinely measured pretreatment (Versant HCV RNA version 3.0; Bayer BV, Mijdrecht, the Netherlands; lower limit of detection of 615 IU/ml) and at weeks 4, 12, 24, 48 and 24 weeks after discontinuation of therapy using the qualitative Roche Amplicor® (lower limit of detection <50 IU/ml; Roche Molecular Systems, Pleasanton, CA, USA), the standard PCR assay performed in our clinic. A null-response was defined as <2 $\log_{10}$ drop in HCV viral load at week 12 of therapy after which PEG-IFN-α monotherapy was discontinued in all but 2 patients who were treated for 24 weeks. An early viral response (EVR) was defined as >2 $\log_{10}$ drop in HCV RNA at week 12 of therapy.

Viral sequencing and IL28B analysis

Total RNA was isolated from plasma using TRIzol reagent (Invitrogen, Breda, the Netherlands), dissolved with RNAse inhibitor (Applied Biosystems, Foster City, CA, USA) and reverse transcribed using an iScript cDNA Synthesis Kit (BioRad, Veenendaal, the Netherlands) according to the manufacturer's protocol. The used mix of primers was purchased from Eurofins MWG Operon (Ebersberg, Germany). PCR products were ligated into the pGEM-T vector and 10–20 clones were sequenced using the M13 primers (Eurofins MWG Operon). Sequences were aligned and analysed using BioEdit (Ibis Biosciences, Carlsbad, CA, USA). Quasispecies were aligned to their reference strain: H77 for genotype 1a, D90208 for genotype 1b, Y11604 for genotype 4a and D86638 for genotype 4d. Phylogenetic trees were constructed by the rooted neighbour-joining method and visualized using MAFFT software (version 6) [33]. The robustness of the phylogeny was assessed by bootstrapping with 100 rounds of replications (values >70 were considered robust clusters).

Peripheral blood mononuclear cells (PBMCs) were isolated from sodium heparin tubes using a Ficoll-Hypaque density gradient centrifugation or with sodium citrate tubes for cell separation (CPT™, BD Biosciences, San José, CA, USA). One million PBMCs were lysed using L6 lysis buffer after which DNA was isolated using standardized isopropanol/ethanol. SNP

genotyping was performed using allelic discrimination assays (Applied Biosystems) for the SNP rs8099917 and rs12979860 following the instructions of the manufacturer. Data were analysed using the ABI PRISM SDS software version 1.7 (Applied Biosystems). All patients provided written informed consent and institutional ethical review boards at participating centres approved the protocol.

Statistical analyses

Data were analysed non-parametrically using a Fisher's exact test. Statistical significance was reached with a *P*-value of ≤0.05 and all tests used were two-sided. All data were analysed using GraphPad Prism (version 4.0 for Windows; GraphPad Software, San Diego, CA, USA).

Results

Of the 23 HIV-infected patients diagnosed with an acute HCV infection in the two centres (UMCU and UMCG) between January 2006 and January 2009, 1 (4%) patient spontaneously cleared the infection while another patient was treated with combination treatment PEG-IFN-α/ribavirin from the beginning (Figure 1). Two patients (one psychologically unfit and one retrospectively diagnosed) were not treated leaving 19 patients for treatment with PEG-IFN-α monotherapy. Patient characteristics of those treated are shown in Table 1. All patients were male and infected with either HCV genotype 1 (68%) or genotype 4 (32%). The HCV viral load was high with a median of 6.49 $\log_{10}$ IU/ml (IQR 5.77–6.70). The time from HCV seroconversion to start of therapy was 12 weeks (IQR 7–16). Nearly half (47%) of the patients were treated for 24 weeks. Patients had a relatively high CD4$^+$ T-cell count (median of 500 cells/mm^3, IQR 300–693) and 8 (42%) patients received combination antiretroviral treatment (cART) for their HIV infection.

Overall, PEG-IFN-α monotherapy was well-tolerated with no dose modifications necessary. Both leukocytopaenia (white blood cell counts below 3.5×10^9/l) and thrombocytopaenia (platelet counts below 150×10^9/l) were generally mild and seen in 53% of patients without the need to administer growth factors. Anaemia occurred in 2 of 3 patients treated with add-on ribavirin, but haemoglobin concentration did not drop below 10 g/dl (6.2 mmol/l). CD4$^+$ T-cell counts dropped below 200 cells/mm^3 in 4 (21%) patients and fully returned to pretreatment values after discontinuation of treatment while no opportunistic infections occurred. All patients finished their anti-HCV treatment as intended and according to laboratory data and patients self-reporting, compliance to PEG-IFN-α monotherapy during the course of treatment was considered to be good.

Treatment outcome

Of the 19 treated patients, 7 (37%) reached an RVR (Figure 1). One of the RVR patients subsequently had a viral rebound with high plasma HCV RNA levels at week 12 and week 24 – effectively being a null-responder and thus therapy was discontinued. After 12 weeks of treatment an EVR was reached by 10 (53%) patients, of which two used add-on ribavirin from week 4 onwards. All these patients achieved an end-of-treatment response (ETR). A total of 9 (47%) patients treated with PEG-IFN-α monotherapy, with 1 patient concurrently receiving add-on ribavirin, failed to respond to therapy and were considered null-responders (<2 $\log_{10}$ drop in HCV RNA from baseline). An SVR was achieved by 7 (37%) patients with 5 of these 7 patients (71%) achieving an RVR and 1 patient using add-on ribavirin. The final outcome is summarized in Figure 2.

A subsequent subgroup analysis of patients being treated with PEG-IFN-α monotherapy without add-on ribavirin (*n*=16) showed a similar clinical outcome with respect to RVR, EVR, ETR and SVR (44%, 50%, 50% and 38%, respectively). Of the three patients with add-on ribavirin, one achieved a SVR while one experienced a relapse and the other one was a null-responder (Figure 1). Although the number of patients with add-on ribavirin was very small, addition of ribavirin to PEG-IFN-α monotherapy at week 4 does not seem to be a successful strategy. Furthermore, a stratified analysis based on the time of treatment initiation showed that 5 of 11 patients (45%), starting treatment within 12 weeks after the diagnosis, achieved an SVR in contrast to 1 of 5 patients (20%) starting therapy thereafter (*P*=0.59). Finally, treatment with cART, baseline CD4$^+$ T-cell counts, baseline HCV viral load and baseline alanine aminotransferase values did not influence acute HCV treatment outcome and were not predictors for achievement of a RVR (JEA *et al.*, data not shown).

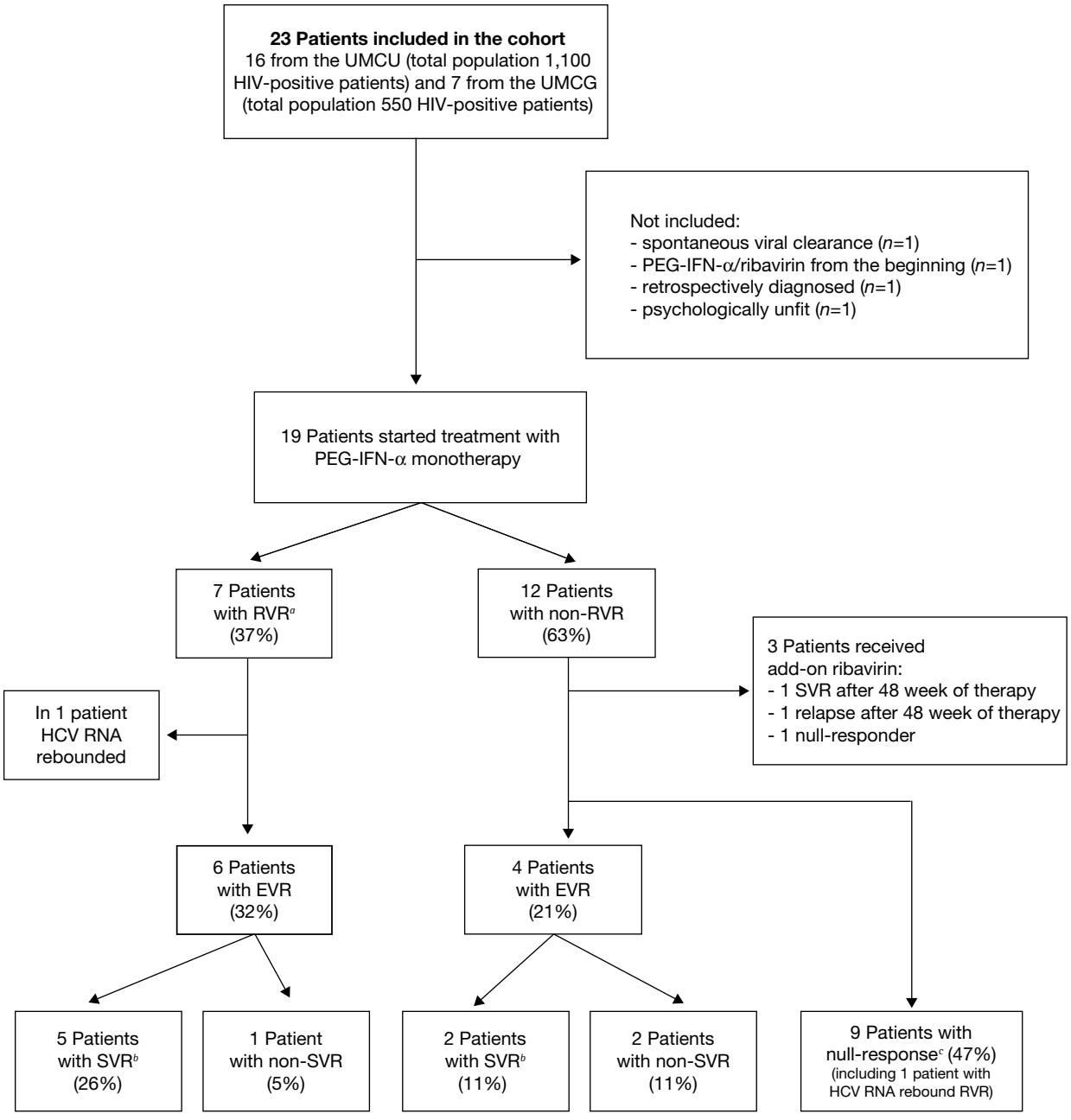
In 5 patients HCV RNA re-emerged after finishing PEG-IFN-α monotherapy (4 with detectable HCV RNA at week 24 and 1 at week 12 after end of treatment with PEG-IFN-α). To differentiate between relapse and re-infection of HCV, NS5B sequence analysis of the quasispecies of these patients was performed. A rooted neighbour-joining phylogenetic tree analysis clearly demonstrated a relapse in 3 out of 5 patients (Figure 3A). Compared with the overall patient cohort, in these relapse patients, no distinctive parameters known to negatively influence the outcome of therapy (such as time from seroconversion to start of treatment, baseline viral load, HIV status or genotype) were found. The other two patients (one achieving an RVR and one with an HCV RNA of 80 IU/ml at week 4 of therapy) were re-infected by their partner since the HCV sequences of the re-infection strains in the patients clustered with the partners' HCV strains. These partners

were both null-responders to acute anti-HCV treatment (that is, null responders in the study cohort; Figure 3B and Additional file 1). Therefore, these two re-infected patients were regarded as sustained responders for the original PEG-IFN-α monotherapy treatment resulting in a total of 7 (37%).

Distribution of IL28B polymorphisms according to outcome of therapy

Given the importance of the recently published IL28B gene SNPs [27], an evaluation of both of the two most strongly associated SNPs [34] (the rs8099917 unfavourable G-allele for response and the rs12979860

Figure 1. Flowchart of the cohort study describing the outcome of HIV-infected patients with acute HCV



[a]Rapid virological response (RVR): HCV RNA<50 IU/ml at week 4 of therapy. [b]Including one patient in each group (total of two) who achieved a sustained virological response (SVR) but was re-infected by his partner. [c]Null-response: HCV RNA<2 $\log_{10}$ drop at week 12 of therapy. EVR, early virological response; PEG-IFN-α, pegylated interferon-α; UMCG, University Medical Center Groningen; UMCU, University Medical Center Utrecht.

favourable C-allele for response) was performed to explain the outcome of PEG-IFN-α monotherapy. The rs8099917 favourable G-allele is the minority allele in the general population and is therefore modelled dominantly, by combining the minor homozygote G/G with the heterozygote G/T leading to two categories for analysis (unfavourable G/G+G/T versus favourable T/T). Although the rs12979860 favourable C-allele is the minor variant worldwide, in the Caucasian population C/C is the dominant genotype and was therefore modelled recessive, combining the minor homozygote T/T with the heterozygote C/T (that is, favourable C/C versus unfavourable C/T+T/T). Of the 12 non-SVR patients, 8 (67%) patients were carriers of the rs8099917 unfavourable G-allele, whereas 4 (33%) patients were homozygous for the favourable T/T-genotype (Table 2). In patients achieving a SVR, 3 and 4 patients were carrier of the G-allele and T-allele, respectively (43% and 57%). The rs12979860 favourable C/C genotype was present in 2 (29%) patients achieving a SVR compared with 5 (71%) SVR patients carrying the unfavourable T-allele (Table 2). In patients without a SVR, the majority of 9 (75%) patients was carrier of the unfavourable T/T genotype compared with only 3 (25%) patients who were carriers of the favourable C/C-allele.

Discussion

This is the largest prospective cohort study of HIV-infected patients with acute HCV to analyse the efficacy of PEG-IFN-α monotherapy. The results of this study are twofold. First, a low SVR rate with PEG-IFN-α monotherapy was observed due to a high percentage of non-response with detailed quasispecies analysis showing both HCV re-infections as well as relapses. Second, the majority of the patients not achieving a SVR were carriers of the unfavourable G-allele of the IL28B SNP rs8099917.

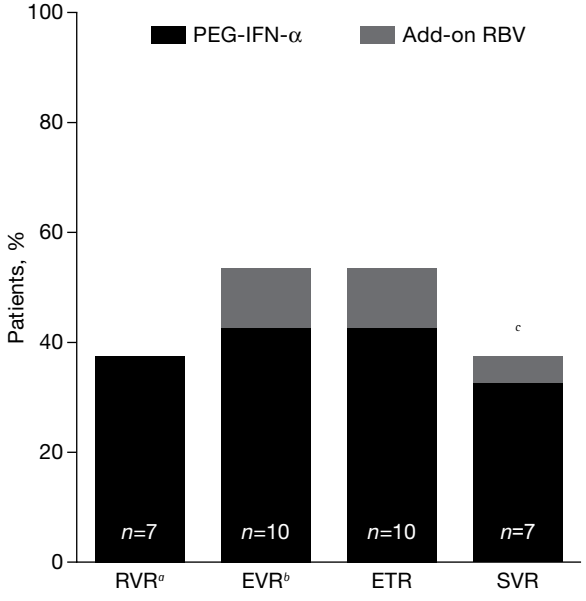
In acute HCV monoinfected patients, high SVR rates varying between 72% and 98%, were reached with PEG-IFN-α monotherapy making addition of ribavirin unnecessary [8,9,35]. As the optimal therapeutic regimen for HIV-infected patients with acute HCV is currently debated [10,11], the current cohort was established demonstrating a low SVR rate of 37% in HIV-infected patients with acute HCV. Retrospective studies and case series on the role of PEG-IFN-α monotherapy, have shown contradictory results with a large variety in SVR rates from 0% [17,22] to 100% [21,23]. A small cohort study treating seven patients with PEG-IFN-α monotherapy for 12 weeks showed an SVR rate of 67% [20]. Two small non-randomized trials comparing PEG-IFN-α monotherapy with PEG-IFN-α/ribavirin therapy reported either higher SVR rates for the latter (40% versus 57%) [25] or the opposite with superior efficacy of PEG-IFN-α monotherapy over combination therapy (80% versus 48%) [24]. This wide variance in SVR rates might be explained by the included HCV genotypes being genotype 1 and 4 (in

Table 1. Baseline characteristics

Patient characteristic	Value (*n*=19)
Age, years	42 (39–48)
Genotypes 1/4	13 (68)/6 (32)
Sex male/female, *n*[a]	19/0
HCV viral load, $\log_{10}$ IU/ml	6.49 (5.77–6.70)
Maximal ALT, U/l	541 (233–849)
Time from seroconversion to start therapy, weeks	12 (7–16)
$CD4^+$ T-cell count, copies/mm^3	500 (300–693)
On antiretroviral therapy[b]	8 (42)
PI-based, *n*	6
NNRTI-based *n*	2
HIV viral load in detectable patients, $\log_{10}$	5.00 (4.83–5.40)

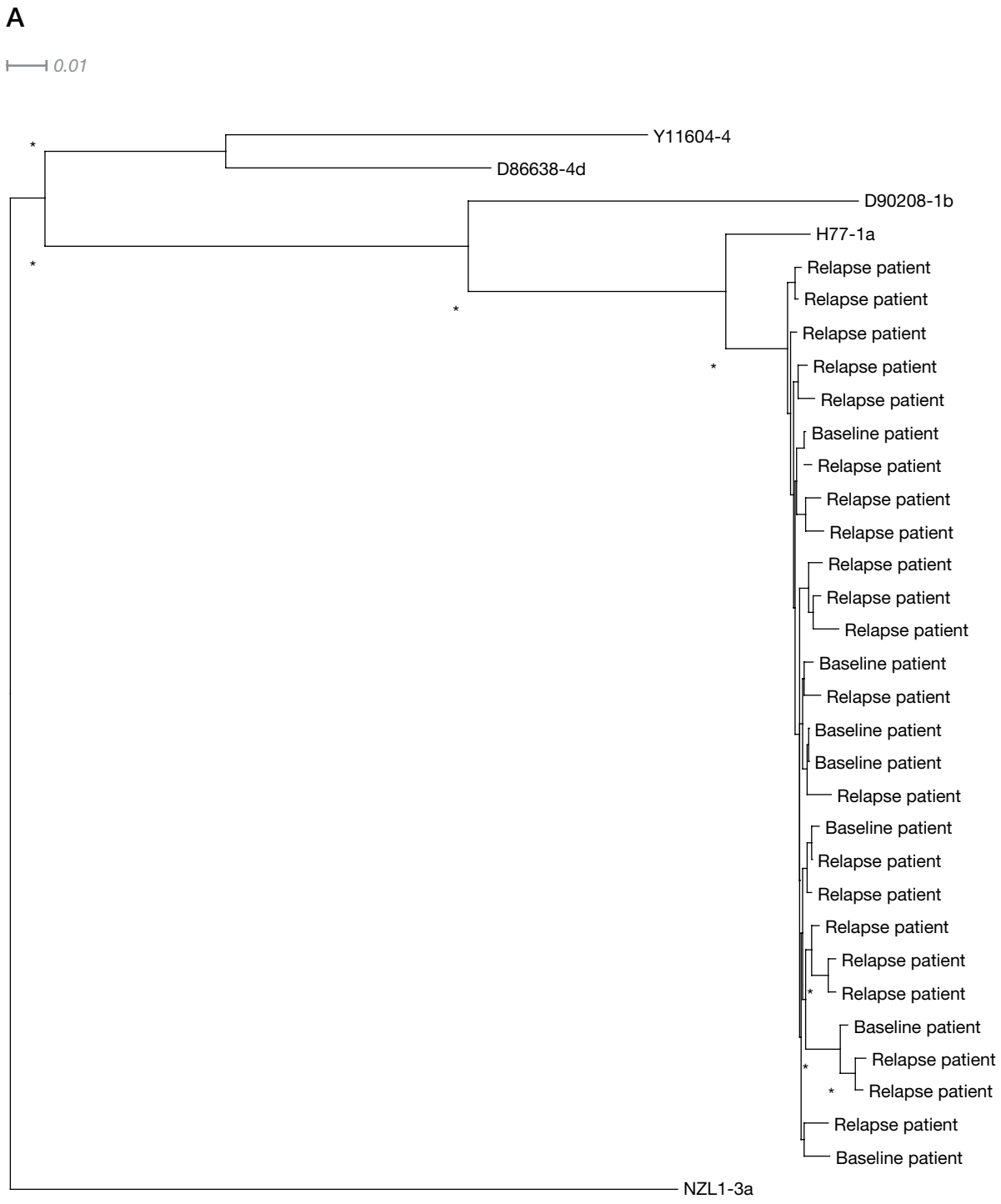
Continuous data are presented as median (IQR) and categorical data are presented with *n* (%) unless otherwise indicated. [a]In all patients the supposed mode of HCV transmission was permucosal (men having sex with men). [b]All eight patients receiving HAART had undetectable HIV viral load (<50 copies/ml). ALT, alanine aminotransferase; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Figure 2. Summary of virological outcome after PEG-IFN-α therapy



Treatment response of all 19 patients treated with pegylated interferon-α (PEG-IFN-α) monotherapy and add-on ribavirin from week 4 onwards. The positive predictive values for sustained virological response (SVR) were [a]83.3% and [b]70% for rapid virological response (RVR) and early virological response (EVR), respectively. [c]Two patients were re-infected by their partner after discontinuation of treatment. ETR, end-of-treatment response; RBV, ribavirin.

Figure 3. Phylogenetic analysis of patients with a HCV relapse and a HCV re-infection



Rooted neighbour-joining phylogenetic tree analysis of **(A)** a patient with an HCV relapse (baseline and relapse strains) and **(B)** a patient with a HCV re-infection from his partner (baseline, re-infection and partner strains) are shown. The reference strains H77-1a and D90208-1b are shown together with multiple strains of thre chronic HCV-infected patients of the same genotype. Bootstrap values of >70 were considered robust and are therefore shown (indicated with asterisks).

Figure 3. Continued

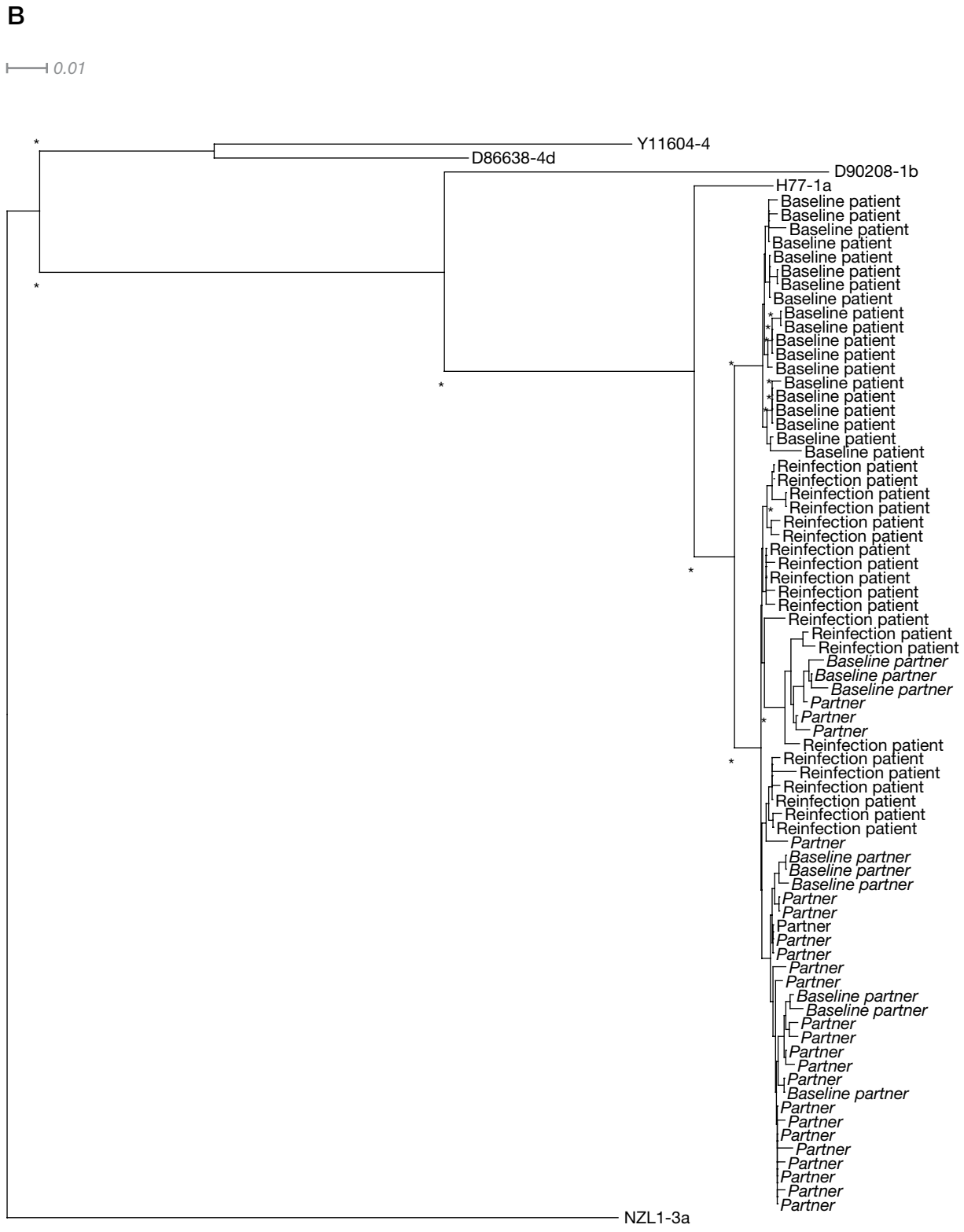


Table 2. Distribution of IL28B polymorphisms according to outcome of acute HCV treatment

SNP	SVR (*n*=7)	Non-SVR (*n*=12)	*P*-value
rs8099917			0.38
G/G+G/T	3 (43)	8 (67)	
T/T	4 (57)	4 (33)	
rs12979860			1.00
C/C	2 (29)	3 (25)	
C/T+T/T	5 (71)	9 (75)	

Categorical data are presented with *n* (%). SNP, single nucleotide polymorphism; SVR, sustained virological response.

majority or exclusively) in studies reporting low SVR rates [19,22,25] and all HCV genotype (including 2 and 3) in studies with higher SVR rates [20,21,23,24]. Alternatively, clustering of all patient HCV strains into one group, suggesting a common source [22], was not observed in this study by phylogenetic analysis. By contrast, most studies investigating the efficacy of combination therapy with PEG-IFN-α with ribavirin reported more consistent SVR rates ranging between 59% and 80% [12–18]. Moreover, in contrast to the varying rates of null-response reported in these studies (5–30%), in our study, as much as 47% of patients proved to be non-responsive to PEG-IFN-α monotherapy. Therefore, this study contributes considerably to the growing body of evidence that PEG-IFN-α/ribavirin combination therapy is the preferred treatment regimen for acute HCV in HIV-coinfected individuals in order to maximize SVR rates.

The large number of non-responders (63%, that is, null-response and relapse) to PEG-IFN-α monotherapy in this study was surprising. The reason for this is most probably multifactorial with viral-, host- and treatment-related factors all being important [36]. One plausible explanation could be that ribavirin was not part of the treatment regimen. Previous treatment studies in chronic HCV–HIV-coinfected patients demonstrated higher SVR rates in patients receiving weight-based ribavirin compared with those taking standard dose ribavirin [37]. Although the working mechanism of ribavirin is still largely unknown [38], it has been suggested that optimizing concentrations of ribavirin both to body weight and plasma levels, will achieve higher SVR rates thus leading to lower relapse rates [39]. The recently discovered SNP in the inosine triphosphatase (ITPA) gene causing ITPase deficiency protecting against ribavirin-induced hemolytic anaemia, might help to optimize future treatment regimens including ribavirin [40]. Therefore, combination of PEG-IFN-α and ribavirin seems necessary to treat acute HCV in HIV-coinfected patients.

Recently, studies have highlighted the importance of molecular markers in relation to non-response to therapy [41]. Genome-wide association studies have revealed several SNPs in the IL28B region to be strongly associated with either spontaneous clearance of acute HCV [26] and successful outcome [27,28] or non-response [29,30] to therapy in chronic HCV. The favourable C/C genotype in the rs12979860 IL28B SNP was shown not to attribute to the SVR rates in HIV-infected patients with acute HCV (73% versus 60%) [42]. Similarly, our study confirmed the observation that IL28B favourable C/C phenotype does not seem to play a role in the treatment-induced viral clearance of acute HCV in HIV-infected patients. However, in this study, the SNP rs8099917 G-allele, was found in the majority of non-responders to treatment and could therefore be an explanation for the high rates of non-response to PEG-IFN-α monotherapy in this cohort. Furthermore, it has been shown in patient with chronic HCV that differential up-regulation of hepatic interferon-stimulating genes was associated with response to PEG-IFN-α/ribavirin therapy [43]. Similar observations have been reported from gene expression profiles of PBMCs [44] underscoring the importance of genetic analyses in future studies of HIV-infected patients with acute HCV.

In contrast to the classical route of HCV transmission (intravenous drug use or needle stick injuries), the current epidemic of acute HCV in HIV-infected MSM indicates that high-risk sexual behaviour is also a possible mode of transmitting HCV [4]. Therefore, when patients continue their high-risk behaviour during or after anti-HCV therapy, in-depth quasispecies analysis should be performed to reliably distinguish between HCV relapse and re-infection. This is clearly shown in two patients in our cohort who denied any unsafe sexual intercourse at the time of recurrence of HCV viraemia. NS5B quasispecies sequencing, but not genotype, line blot analysis and population sequencing, did discriminate between re-infection or relapse. As SVR rates of re-treatment of HCV relapse are much lower than for treatment-naive infections (that is, in case of re-infection), discriminating between these entities is important from both a patient and a physicians perspective.

In conclusion, PEG-IFN-α monotherapy is insufficient for the treatment of acute HCV in HIV-coinfected patients. Furthermore, detailed quasispecies analysis is

important in this high-risk population to distinguish relapse from re-infection. Lastly, a polymorphism in the IL28B gene was associated with non-response in this population.

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JEA, SvA and AIMH contributed to the design of the cohort, the data analyses and wrote the manuscript. CJS contributed to the data analyses. AMJW contributed to the virological analyses. JHF contributed to the IL28 polymorphism analyses. IMS and SNMS contributed to the sequence analyses. TM contributed to the design of the cohort and to the data analyses. DvB contributed to the IL28 polymorphism analyses and wrote the manuscript. HGS contributed to the design of the cohort and to the data analyses. Part of this work was presented as a poster (number 2458) at the *49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*, 12–15 September 2009 in San Francisco, CA, USA.

Disclosure statement

AIMH has received a research grant from Roche BV, the Netherlands. JEA, SvA, CJS, AMJW, JHF, IMS, SNMS, TM, DvB and HGS declare no competing interests.

Additional file

Additional file 1: A phylogenetic comparison between an acute HCV reinfection in an HIV-infected patient from the cohort and random HCV sequences of 16 HCV-infected patients from the UMCU can be found at http://www.intmedpress.com/uploads/documents/AVT-10-OA-1872_Arends_Add_file1.pdf

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