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HCV RNA decline in the first 24 hours exhibits high negative predictive value of sustained virologic response in HIV/HCV genotype 1 co-infected patients treated with peginterferon and ribavirin

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Summary

Background—Treatment with Peg-interferon and ribavirin (PEG-IFN/RBV) for HIV patients co-infected with hepatitis C virus (HCV) genotype 1 has suboptimal rates of response. Viral kinetics has emerged as one of the best prognostic factors of treatment outcome.

Methods—Twenty HIV/HCV genotype 1 co-infected patients in treatment with PEG-IFN/RBV, had blood drawn at baseline, 24h, 4, 12, 24, 48, and 72 weeks. HCV-RNA levels were evaluated at each time point. ROC curves were used to evaluate the $\log_{10}$ HCV-RNA decay at 24h that exhibits the best predictive value of achieving response. Genomic characterization of HCV NS5A at both interferon sensitivity-determining region (ISDR) and protein-kinase binding (PKRBD) domains were performed in order to evaluate its heterogeneity and association with 24h HCV-RNA decay and SVR.

Results—Non-responder patients exhibited a mean of $0.7\log_{10}$ (SD $0.74\log_{10}$) HCV-RNA decay at 24h, whereas responder-patients presented $1.6\log_{10}$ (SD $0.28\log_{10}$), p=0.04. A reduction in HCV viral load from baseline to 24h of <1.4 had a negative predictive value for achieving SVR of 100% and a positive predictive value of 50%. HCV genotype 1 isolates from patients with a decrease of HCV-RNA at 24h >$1.4\log_{10}$, exhibited 3.1(SD 1.5) amino acids substitutions in ISDR and 4.8(SD 2.3) in PKRBD regions and 1.6(SD 0.7) and 2.4(SD1.3), respectively, in those patients presenting lower reduction in HCV-RNA.

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Conflict of interest:
The authors do not have any commercial or other association that might pose a conflict of interest.

Conclusions—HIV/HCV genotype 1 co-infected patients with a decrease in HCV-VL at 24h >1.4 $\log_{10}$ are more likely to achieve SVR when treated with PEG-IFN/RBV than those with lower levels of HCV-RNA decay. Along with other host-related and viral-related prognostic factors in HIV/HCV co-infected patients, this very early time point of evaluation could be of relevance in the management of HCV-specific treatment.

Keywords

24h; viral kinetics; SVR; HIV/HCV co-infection; HCV treatment; NS5A

1. INTRODUCTION

Around 20% of the people living with HIV/AIDS worldwide are co-infected with HCV (Soriano et al., 2010); similar rates of co-infection have been observed in Argentina (Laufer et al., 2010).

In the context of highly active antiretroviral therapy, chronic hepatitis C has emerged as one of the leading causes of morbidity and mortality in HIV patients, mainly in developed countries (Rockstroh et al., 2005; Weber et al., 2006). The combination of Pegylated interferon (PEG-IFN) and ribavirin (RBV) is the best available treatment for chronic HCV infection both in HCV monoinfected patients and in those co-infected with HIV (Chung et al., 2004). However, this treatment results in sustained virological response (SVR) in less than 50% of co-infected patients (Chung et al., 2004).

Virological response kinetics has emerged as one of the best prognostic factors of treatment outcome (Van den Eynde et al., 2009). HCV kinetics studies during treatment with PEG-IFN, showed that HCV-RNA generally declines with a biphasic pattern, consisting of a rapid first phase lasting for approximately 1-2 days, followed by a second phase less pronounced of HCV-RNA decline (Dahari et al., 2008). There is increasing evidence that early time points during treatment, such as HCV viral load at weeks 2 and 4 can be used to guide and individualize therapy in both HCV-monoinfected and HIV/HCV-co-infected patients (Neumann et al., 2009). Furthermore, a correlation has been observed between HCV- RNA decline in the first 48 hours of treatment and SRV in monoinfected patients (Durante-Mangoni et al., 2009); however, this correlation remains controversial in the presence of HIV co-infection(Arends et al., 2009; Araújo et al., 2010).

Both host and viral factors influence the response to specific antiviral treatment (Kau et al., 2008). The main host factors that affect the rate of SVR are age, body mass index, liver fibrosis, and insulin resistance (Bortoletto et al., 2010). IL28B-associated polymorphisms is also a host factor that has been linked with response to therapy (Ge et al., 2009; Thomas et al., 2009). High baseline viremia, HCV genotype (Lindh et al., 2010) and mutation in NS5A region have been described as viral factors influencing HCV therapy outcome (Kau et al., 2008). The NS5A protein of HCV has the potential to block IFN-induced RNA-dependent protein kinase (PKR) and may therefore interfere with the response to IFN therapy. More than 4 mutations in the NS5A PKR-binding domain (PKR-BD) have been associated with responsiveness to IFN-alfa. Specifically inside the PKRBD, the Interferon Sensitivity Determining Region (ISDR) has been described to interfere with HCV viral response to IFN (El-Shamy et al., 2008; Enomoto et al., 1996).

The present analysis evaluates the predictive value for SVR of HCV viral load (HCV-VL) decline at 24 hours of initiation of PEG-IFN/RBV therapy in a cohort of 20 HIV/HCV genotype 1 co-infected individuals. We have also studied the association of 24 hour decay of

HCV RNA with baseline host factors as well as viral characteristics including HCV genotype 1-NS5A genomic heterogeneity at the PKR-BD.

2. METHODS

2.1 Patients and samples

This is a prospective cohort study of HIV patients co-infected with HCV genotype 1, from a single hospital in Buenos Aires, Argentina, treated in 2007 and 2008 with PEG-IFN and RBV. The protocol was approved by the ethics committee at the Universidad de Buenos Aires. Patients that gave their informed consent were included in the analysis if they met the following inclusion criteria: infection with HCV genotype 1, previously untreated chronic hepatitis C with PEG-IFN and ribavirin, positive HCV-RNA in plasma, ALT higher than 1.5 fold upper normal limit; CD4+ cell count above 200 cells/mm3 and HIV viral load below 50,000 copies/mL, in response to a stable antiretroviral treatment or without antiretroviral treatment if not required by the current national guidelines. Exclusion criteria included: presence of other causes of liver disease, decompensated cirrhosis, pregnancy and potential contraindications for interferon or for ribavirin therapy like hemoglobinopathies, cardiopathy, autoimmune diseases, major depression or other severe psychiatric pathologies, as well as active drug consumption within the last twelve months. A total of 20 patients were included.

Treatment was planned for 48 weeks in all patients. Fifty percent of patients received subcutaneous PEG-IFN alfa-2b (Peg-Intron-A, Schering Corp, Kenilworth, NJ) (80mcg-150mcg, body weight-adjusted dosing) each week plus oral ribavirin (Rebetol, Schering Corp, Kenilworth, NJ) every day; and 50% of patients received subcutaneous PEG-IFN alfa-2a (Pegasys, Roche Corp, Hertfordshire, UK) (180mcg) each week plus daily oral ribavirin (Copegus, Roche Corp, Hertfordshire, UK). RBV dosing was body weight-adjusted in all cases: 800mg when the body weight was below 60kg, 1000 mg when it was between 60-75kg and 1200 mg when body weight was above 75kg. When at least a 2log reduction in HCV RNA at week 12 was obtained, patients continued treatment and were re-evaluated at week 24; if HCV RNA was not detectable, treatment was continued until week 48.

2.2 Monitoring

Patients were evaluated before beginning treatment, at 24 hours, 2 weeks after starting therapy and every 4 weeks until the cessation of therapy, and 24 weeks after the end of treatment to evaluate SVR. Blood samples were drawn at baseline, 24 hours, 4, 12, 24, 48, and 72 weeks. HCV-VL (Bayer VERSANT® HCV RNA 3.0 Assay, range 615 to 7690000 IU/mL)) and HCV qualitative PCR (Cobas Amplicor HCV 2.0, lower limit of detection 50 IU/ml) were evaluated at each time point. Genotype was evaluated with Versant HCV Genotype 2.0 Assay (LiPA). Plasma samples were frozen at -80°C until use.

2.3 RT-PCR and direct sequencing of the HCV NS5A region

HCV RNA was extracted from 200 μl of pre-treatment plasma by Trizol LS (GIBCO,Life Technologies) from 19 of the 20 baseline isolates. Isolated HCV-RNA was reverse transcribed using MMLV Reverse Transcriptase (Invitrogen) in the presence of NS5A antisense primer.

NS5A amplifications were performed as previously described (Bolcic et al., 2008). Amplification products were sequenced by the use of Big Dye Terminator Kit v.3.0 (Applied Biosystems) in the ABI Prism 3100 automatic sequencer (Applied Biosystems).

2.4 Sequence analysis

Sequences of all samples were edited with Sequencher software v.4.10.1 (Gene Codes) and aligned with Mafft program (http://mafft.cbrc.jp/alignment/server/). Nucleotide sequences were translated into amino acid sequences. The aminoacidic substitution number of NS5A PKRBD were visually counted and compared with the HCV genotype 1a prototype M62321.

2.5 HCV viral load analysis

The following definitions were used to analyze the HCV kinetics in the present study. Rapid virological response (RVR) was considered when HCV RNA was undetectable by a qualitative technique (lower limit of detection 50 IU/mL) at week 4. Partial early virological response (pEVR) was defined as a $2\log_{10}$ HCV-VL decay from baseline at week 12 of treatment, and complete early virological response (cEVR) was defined as an undetectable HCV viral load (quantitative technique, lower limit of detection 615 IU/mL) at the same week. Twenty-four weeks response, end of treatment response (ETR) and sustained viral response (SVR) were defined as undetectable HCV RNA by a qualitative technique (lower limit of detection 50 IU/mL) at weeks 24, 48 and 72, respectively. Finally, 24 hours HCV RNA change was calculated as the decrease in HCV-VL from baseline at 24 hours: $\Delta 24\text{-}\ 0 = \log_{10} V24 - \log_{10} V0$. V24 describes the HCV viral load at 24 hours and V0 the viral load at baseline.

2.6 Statistical analysis

A descriptive analysis of baseline variables was conducted looking at the central tendency and dispersion. These values were compared with the aim of evaluating if the demographic, epidemiological, clinical, biochemical and histopathological characteristics were similar among patients who achieved SVR and those who did not. Fisher's Exact Test was used to analyze qualitative variables and Mann-Whitney U test to analyze quantitative variables. The significance level was set at 5% and all tests were 2-tailed. The area under the receiving operating curve (AUROC) was used to calculate the cut-off point in viral load decline at 24 hours with the best sensitivity, negative and positive predictive value.

Statistical analyses were performed using SPSS v.12.0 (SPSS Corporation, Chicago, IL) and Medcalc (Demo version 10.0.2.0).

3. RESULTS

Twenty HIV/HCV-genotype 1 co-infected patients were prospectively included in this study. Demographic, virological, immunological and clinical characteristics are described in Table 1. Patients received either PEG-IFN alfa 2a or 2b, depending on the drug provision by the Argentinean Ministry of Health. Ninety percent of the subjects were on HAART, all of them with undetectable HIV viral load. Forty-five percent of them received abacavir-based HAART. A negative drug-drug interaction between abacavir and ribavirin has been postulated by some authors (Vispo et al., 2008), but this effect seems to be negligible when the ribavirin dose is adjusted to patient's weight (16 mg/Kg) (Amorosa et al., 2010; Laufer et al., 2008; Vispo et al., 2008).

Only one patient reached rapid virological response. Complete EVR was achieved in 25% of the cases; 25% reached only pEVR but all these patients presented detectable HCV-RNA at week 24 and treatment was stopped. Two patients discontinued treatment prematurely for adverse events (thrombocytopenia).

Sustained virological response was obtained by 15% of the patients and there were no differences regarding baseline CD4+ cell count, age, body weight, years of known HIV or HCV infection, use of abacavir, tenofovir or efavirenz and fibrosis on liver biopsy (Table 1).

3.1 HCV 24 hours kinetics

To evaluate the early kinetic of HCV RNA decline, the viral load at 24 hours of treatment initiation was quantified. HCV-VL decay in the first 24 hours of treatment was associated with the achievement of complete early virological response, 24 weeks response and end of treatment response (Table 2). No differences were found in baseline characteristics of patients who achieved or not these time points of response (Table 1).

When HCV RNA decay at day 1 was compared between patients who only exhibit a $2\log_{10}$ reduction in HCV-VL at week 12 (ie: partial EVR) and those with null response (ie: $<2\log_{10}$ reduction in HCV-Vl at week 12) no differences were found (pEVR $0.64\log_{10}$, SD 0.54 $\log_{10}$ and NR $0.71\log_{10}$, SD $0.82\log_{10}$; p=0.79) (Figure 1). Of note, none of the patients that exhibited only pEVR reached SVR.

3.2 24h HCV- VL decay as predictor of SVR

Patients who achieved SVR present a 24h a decay in HCV-VL of 1.6log10 (SD 0.28 $\log_{10}$), whereas those who did not achieved SVR reached only a $0.70\log_{10}$ (SD $0.74\log_{10}$) reduction in HCV RNA, p=0.04.

The kinetic of HCV RNA decay during treatment according to the achievement of SVR is shown in Figure 2.

To assess the predictive value of HCV RNA decay on the first day after treatment initiation with pegylated interferon and ribavirin, we calculated the area under the receiving operating curve (AUROC) of the difference between HCV-VL ($\log_{10}$) at baseline and at 24 hours. We found that AUROC was 0.902 (SD 0.123), 95% confidence interval 0.68-0.98 (p=0.001). A reduction in HCV-VL from baseline to 24h <1.4 had a negative predictive value for achieving SVR of 100% and a positive predictive value of 50%. Using a cut-off value of 1.5 $\log_{10}$ reduction, the negative predictive value decreased to 94.1% whereas the positive one increased to 66.7% (Figure 3). When the two patients who had to stop treatment prematurely due to adverse events were excluded from the analysis, the cut-off value of $1.4\log_{10}$ decay as well as the positive and negative predictive value did not change.

3.3 24 hour HCV viral load decrease and HCV baseline molecular characteristics

Deduced amino acid substitution number of NS5A PKRBD from 19 baseline isolates from the 20 HIV patients were counted and compared with the HCV genotype 1 prototype (M62321) (Figure 4). We observed that HCV viral isolates, from those patients that exhibited a 24h viral load decrease higher than 1.4 $\log_{10}$ and SVR, presented a higher number of amino acid substitutions in ISDR and PKRBD regions than those who did not achieve these goals. This association was statistically significant (p= 0.02 and 0.03, respectively).

Viral isolates from patients with a decrease higher than 1.4 log at day 1 of treatment, exhibited a mean of 3.1 (SD 1.5) amino acids substitutions in ISDR and 4.8 (SD 2.3) in PKRBD regions and those who presented a lower reduction in HCV-RNA had 1.6 (SD 0.7) and 2.4 (SD1.3) amino acid substitutions, respectively (p=0.02 and 0.03). When the number of substitutions were evaluated in relationship with the achievement or not of SVR the results were: for ISDR region 4 (SD 1.7) vs. 1.7 (SD 0.7), p=0.05 and for PKRBD region 6 (SD 2.6) vs. 2.7 (1.4), (p=0.03).

It was also identified with AUROC (0.885, SD 0.132, 95% CI 0.656-0.981, p=0.0035) that the presence of more than 5 amino acid substitutions in PKRBD region had a 100% positive predictive value and 94.1% negative predictive value for achieving SVR. Regarding mutations in the ISDR region, the same negative and positive predictive values were found when 3 or more substitutions were present (AUROC, 0.865, SD 0.141, 95% CI 0.631-0.974, p=0.0099).

4. DISCUSSION

Current guidelines recommend treatment discontinuation if at least a 2log decay in HCV-RNA is not achieved at week 12 (Ghany et al., 2009; Soriano et al., 2007). RVR is not used to guide early therapy discontinuation because it has a very high positive predictive value, though not a negative one.

The results obtained in our study suggest that the decay in HCV RNA as early as the first day after treatment initiation in HIV/HCV genotype 1 co-infected patients could be the first indicator of treatment success, exhibiting 100% negative predictive value of achieving SVR, resembling the predictive value of EVR.

Moreover, we have found that 24 hour viral load decay not only correlated with the achievement SVR in the group of HIV/HCV genotype 1 co-infected patients but also was associated with HCV mutation in ISDR and PKRBD region that have already been described as favorable pretreatment factors of response to therapy (El-Shamy et al., 2008; Enomoto et al., 1996).

One important issue regarding our results was the overall low rate of SVR (15%) and especially of RVR (5%). Most of the subjects included in the study were Latinos, and treatment success has been shown to be lower in this population (Rodriguez-Torres et al., 2009). Other factors that could influence the low rate of response are the very high baseline HCV viral load (60% of patients with more than 600,000 IU/mL) and the high index of liver fibrosis (50% with METAVIR F3-F4). The contribution of the genetic variation in the interleukin 28B (IL28B) gene as a predictor of treatment outcome in genotype 1 HCV-HIV co-infected patients, deserves further investigation in the population under study.

Although the mean of LT-CD4+ cell count in this group of patients with a long history of known HIV infection was higher than 200cells/μL, the specific anti-HCV immunity was not evaluated. Adherence to treatment was high in all the patients included in the study, and dose reduction was only necessary in the two patients that stopped treatment prematurely due to thrombocytopenia.

In HCV-monoinfected patients, it has been observed that 48 hour HCV viral load decay exhibits a high negative predictive value of reaching SVR, but the utility of this very early time point evaluation among/in HIV/HCV-co-infected subjects is still controversial (Arends et al., 2009). Arends et al., did not find an association between the early HCV RNA decay and SVR but the number of co-infected individuals included in the study was too small (n=9). In the cohort of HIV/HCV co-infected patients followed by Araújo et al., it was observed that 48h HCV-VL decay predicts the lack of SVR, but 50% of patients included in this study were infected with HCV genotype 3 and 20 percent of subjects discontinued treatment prematurely (Araújo et al., 2010). In our study we have only included patients infected with HCV genotype 1 with 2 early drop-outs and we found a statistically significant association of 24 hour viral load decay and all the time points evaluated (EVR; ETR; SVR).

The present study was not powered to validate the viral load reduction at 24 hour as a stopping point. Nevertheless, our data provides further evidence regarding the importance of

early kinetics to guide and individualize HCV therapy in co-infected patients. If these observations are confirmed, a more cost-effective resource allocation regarding HCV treatment could be allowed in resource limited settings such as Argentina, where according to the HIV/AIDS program from 2007-2009 only 305 PEG-IFN/RBV treatments were initiated nationwide in co-infected individuals (MSAL, 2009). This could also avoid unnecessary exposure to interferon and ribavirin to subjects that will not reach SVR.

In conclusion, HIV/HCV genotype 1 co-infected patients exhibiting more than $1.4Log_{10}$ decrease in HCV-VL at 24 hour are more likely to achieve SVR when treated with pegylated-interferon and ribavirin. Along with other host-related and viral-related prognostic factors in HIV/HCV co-infected patients this very early time point of evaluation could be of relevance in the management of HCV-specific treatment.

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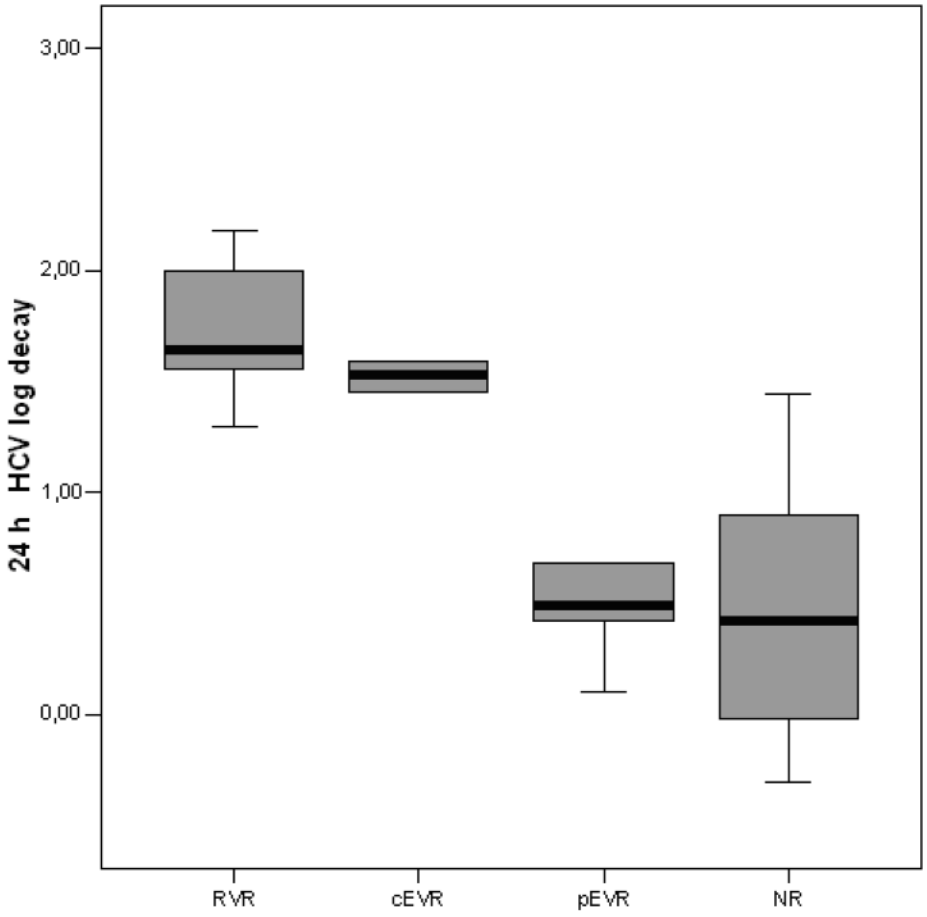

Figure 1.
HCV 24h viral load decrease (median and range) according to the achievement of RVR, EVR (complete and partial), SVR and null response (NR).
cEVR: complete early virological response; pEVR: partial early virological response; RVR: rapid virological response; NR: null response

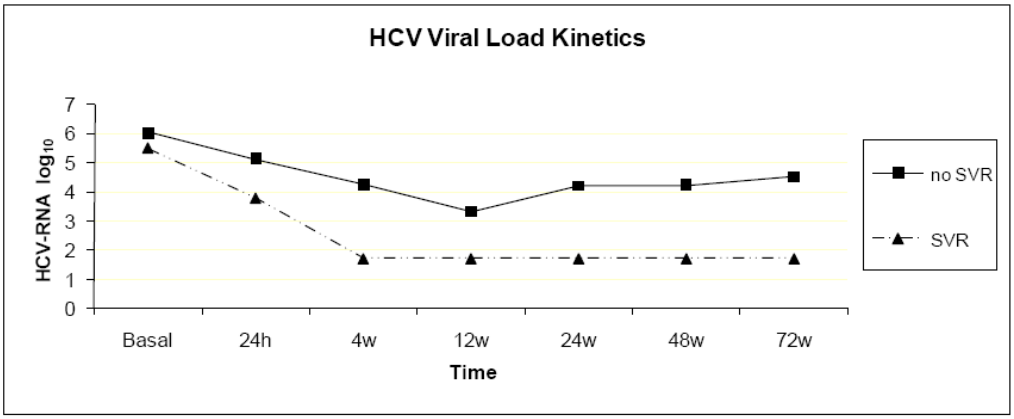

Figure 2.
HCV viral load kinetics during treatment with PEG-IFN/RBV divided by viral response. SVR: sustained virological response. No SVR: absence of sustained virological response.

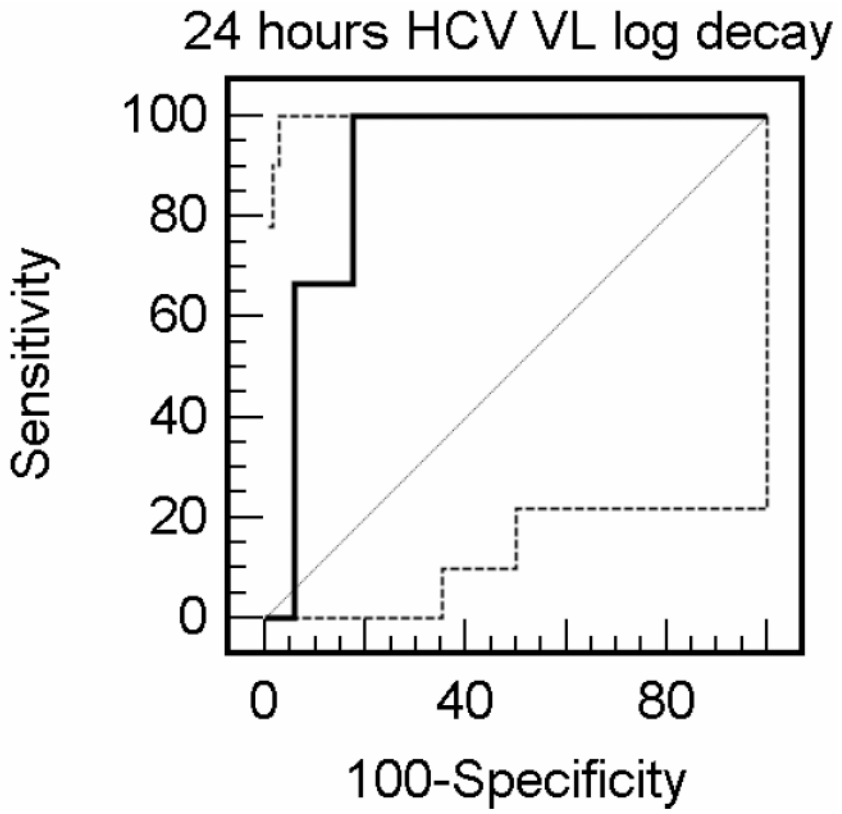

Figure 3.
Area under the receiver operating characteristic curve, to evaluate the performance of HCV-RNA $\log_{10}$ decay at 24h with sustained virological response as the state variable.

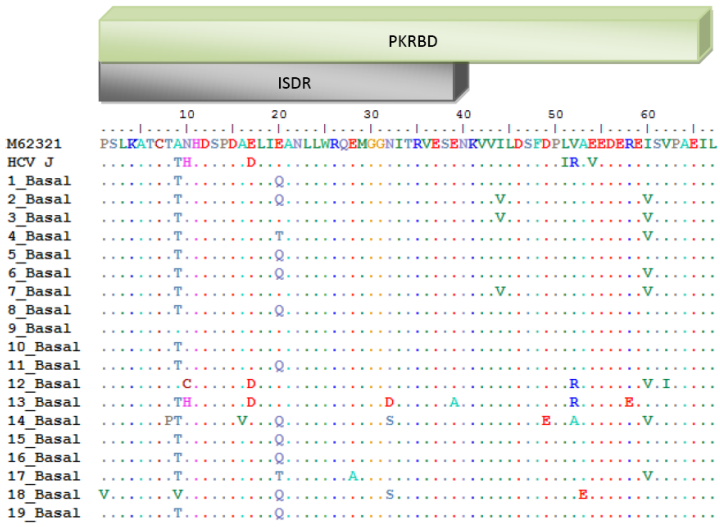

Figure 4.

Basal HCV ISDR and PKRBD amino acids sequences of 19 HCV-HIV co-infected patients. Patients 6, 13 and 14 were SVR, and 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 15, 16, 17, 18 and 19 were NR. M62321 were used as references sequences to compare mutations. HCV-J (D90208) also was included.

Table 1

Baseline characteristics of the total population and divided according the achievement of cEVR, ETR and SVR.

	All	cEVR			ETR			SVR		
	N=20	YES (n=5)	NO (n=15)	*p*	YES (n=4)	NO (n=16)	*p*	YES (n=3)	NO (n=17)	*p*
Age (years) [a]	40.5(4.8)	40(5)	40(5.3)	0.93	40.5(5.7)	40.6(5.1)	0.85	42(5.5)	40.3(5.1)	0.61
Baseline weight (kg)[a]	71.3(12.3)	71(12.9)	71.4(12.5)	0.86	68.5(13.5)	72(12.3)	0.70	71.3(15)	71.3(12.3)	0.92
Ribavirin (mg)[a]	1130(134)	1120(178)	1133(123)	0.93	1100(200)	1137(120)	0.89	1066(230)	1141(117)	0.68
Ribavirin (mg/kg)[a]	16(2.1)	15.9(2.3)	16.1(2.14)	0.55	16.2(2.5)	16.0(2.1)	0.82	14.9(0.1)	16.2(2.2)	0.25
Baseline ALT (IU/mL)[a]	73.2(29.7)	73.6(45)	73.0(24.8)	0.80	70.0(51.2)	74.0(24.3)	0.56	76.3(60.8)	72.6(24.2)	0.83
Baseline CD4 TL (cell/μL)[a]	521(218)	662(261)	474(189)	0.16	589(233)	504(219)	0.55	498(182)	525(229)	0.92
Baseline CD4 TL (%)[a]	27(13.2)	26.8(13.2)	23.7(9.65)	0.50	25.3(11.2)	23.7(7.9)	0.96	20.3(4.9)	25.8(11.1)	0.54
Duration of HCV infection(years)[a]	8.6(5.6)	9.2(2.7)	8.4(6.24)	0.53	8.7(3.1)	8.5(6.0)	0.71	9.0(4.2)	8.5(5.8)	0.65
Duration of HIV infection(years)[a]	10.6(4.3)	12.2(1.6)	10.1(4.9)	0.30	12.5(1.7)	10.1(4.7)	0.25	13(1.7)	10.2(4.6)	0.21
Baseline HIV VL<50 cp/mL [b]	18(90)	5(100)	13(86)	0.50	4(100)	14(87.5)	0.45	3(100)	15(88.2)	0.53
Male gender [b]	18(90)	4(80)	14(93)	0.39	3(75)	15(93.8)	0.26	2(66.7)	16(94.1)	0.14
Baseline HCV VL >600,000 IU/ml [b]	12(60)	2(40)	10(66.7)	0.29	2(50)	10(62.5)	0.64	1(33.3)	11(64.7)	0.30
Fibrosis METAVIR 3-4 score [b, c]	9(50)	2(40)	7(46.7)	0.52	1(50)	8(50)	1.00	1(50)	8(50)	1.00
HAART with abacavir [b]	9(45)	2(40)	7(46.7)	0.79	2(50)	7(43.8)	0.82	1(33.3)	8(47.1)	0.66
HAART with tenofovir [b]	9(45)	3(60)	6(40)	0.43	2(50)	7(43.8)	0.82	2(66.7)	7(41.2)	0.41
HAART with efavirenz [b]	9(45)	3(60)	6(40)	0.43	2(50)	7(43.8)	0.82	1(33.3)	8(47.1)	0.66
Pegylated-Interferon alfa 2b [b]	10(50)	4(80)	6(40)	0.12	3(75)	7(43.8)	0.26	6(85.7)	8(44.4)	0.09

[a] Mean (Std. Desv);

[b] Number (%). ARV: antiretroviral, IDU: intravenous drug user, VL: viral load, HAART: highly active antiretroviral therapy.

[c] There is no liver biopsy available from 2 patients.

Table 2

HCV 24h viral load decay (mean and SD) according to EVR, 24 weeks response, ETR (48 weeks).

	24h HCV-VL decay [mean (SD)]	p
cEVR	1.83 (0.47)	0.001
No cEVR	0.52 (0.54)	
24w negative HCV RNA	1.91 (0.51)	0.005
24w positive HCV RNA	0.58 (0.58)	
48w negative HCV RNA	1.91 (0.51)	0.005
48w positive HCV RNA	0.58 (0.58)	

cEVR: complete early virological response; ETR: end of treatment response; w: weeks, HCV-VL: hepatitis C viral load.