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Insulin resistance predicts re-treatment failure in an efficacy study of peginterferon-α-2a and ribavirin in HIV/HCV co-infected patients

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Background & Aims: Few studies evaluated the efficacy of HCV re-treatment and the predictors of response in HIV/HCV co-infected patients. The role of insulin resistance as a predictor of response in this population is unknown. The aim of this study is to evaluate the safety and efficacy of pegylated interferon-α-2a and ribavirin in re-treatment of HIV/HCV co-infected patients, predictors of sustained virological response, including insulin resistance, and the relationship between insulin resistance and liver histology.

Methods: This prospective, multi-centered study included HIV/HCV co-infected patients with prior interferon-based treatment failure. Patients received pegylated interferon-α-2a and ribavirin for 48 weeks. Serum HCV RNA was measured 24 weeks post treatment to assess sustained virological response. Insulin resistance was defined as HOMA-IR >2. Correlations between baseline insulin resistance and steatosis, and/or cirrhosis were determined.

Results: Sustained virological response was achieved in 14/96 (15%) patients. 35% of patients with HOMA-IR <2 (6/17) achieved sustained virological response vs 14% (5/36) of those with HOMA-IR between 2–4, and 7% (3/41) of those with HOMA-IR >4 ($p = 0.01$). In multivariable analysis, insulin resistance and $\log_{10}$ HCV RNA were negatively associated with sustained virological response [AOR 0.17; 95% CI 0.05–0.64, $p = 0.009$, and AOR 0.36; 95% CI 0.14–0.93, $p = 0.04$, respectively]. Steatosis and cirrhosis correlated with insulin resistance ($p = 0.02$ and 0.03, respectively) but neither independently predicted sustained virological response. Discontinuations due to severe adverse events occurred in 8% of cases, and 2 patients died of unrelated causes.

Conclusions: In HIV/HCV co-infected patients undergoing re-treatment, sustained virological response rate is low; those patients without insulin resistance are significantly more likely to achieve sustained virological response.

Keywords: Insulin resistance; Hepatitis C virus; Chronic; HIV; Re-treatment; Antiviral therapy; Pegylated interferon alfa-2a; Ribavirin.

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Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HRN, hepatitis Resource Network; HCV RNA, hepatitis C virus ribonucleic acid; HOMA-IR, homeostasis model of assessment of insulin resistance; AOR, adjusted odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; SVR, sustained virological response; PegIFN, pegylated interferon; RBV, ribavirin; IR, insulin resistance; IFN, interferon; HIV RNA, human immunodeficiency virus ribonucleic acid; ART, antiretroviral therapy; ULN, upper limit of normal; Hb, hemoglobin; HbA1c, hemoglobin A1c; TSH, thyroid-stimulating hormone; pEVR, partial early virological response; cEVR, complete early virological response; EOT, end of treatment; IRB, institutional review board; HAI, histology activity index; BMI, body mass index; IQR, interquartile range; OR, odds ratio; SAE, severe adverse event; RVR, rapid virological response; ACTG, AIDS Clinical Trials Group; SOCS3, suppressor of cytokine signaling 3; IRS-1, insulin receptor substrate 1; STAT-1, signal transducers and activators of transcription 1.

Introduction

Co-infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) affects an estimated 10 million people worldwide. HCV-related liver disease is now a leading cause of death among HIV-infected patients [1,2]. Successful treatment of HCV is associated with reduced liver-related complications, including liver decompensation, hepatocellular carcinoma (HCC), and liver-related mortality [3,4].

The goal of HCV treatment is to achieve sustained virological response (SVR), defined as undetectable serum HCV RNA 24 weeks after the end of treatment. The current standard of care is 48 weeks of peginterferon-α (pegIFN) and ribavirin (RBV; fixed dose for HCV genotypes 2 and 3, and weight-based for HCV genotypes 1 and 4). However, SVR is achieved in less than half of HIV/HCV co-infected patients in both initial and re-treatment of HCV. In initial HCV treatment, the combination of pegIFN and weight-based RBV has lead to SVR in 22–35% of patients with HCV

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genotypes 1 and 4 [5,6] and 53–72% of patients with HCV genotypes 2 and 3 [6,7]. Despite the high rate of failure of initial HCV treatment regimens, few studies have been done on re-treatment of HCV in co-infected non-responders. The studies that have been published were small and reported overall SVR rates of 16–31% [8–11]. In addition, predictors of SVR in re-treatment have not been well studied.

HIV/HCV co-infected patients, who had failed to respond to a previous course of HCV treatment, were enrolled in an open-label, phase IIIb study (Hepatitis Resource Network (HRN)-004) to evaluate safety, tolerability, and efficacy of pegIFN-α-2a and RBV in re-treatment. In addition, we prospectively evaluated predictors of SVR including baseline insulin resistance (IR). Finally, we examined the relationship between baseline IR and liver histology (steatosis and cirrhosis).

Patients and methods

Patients

Patients were recruited at 10 centers in the United States from August 2002 to June 2005. Eligible patients were co-infected with HIV and HCV and had either relapsed or not responded to prior IFN-based treatment. Chronic HCV infection was defined as a positive HCV antibody test for at least 6 months and detectable serum HCV RNA. HIV-related criteria included patients with either (i) $CD4^+$ T-cell count <100 cells/mm^3 and HIV RNA level <25,000 IU/ml, or (ii) $CD4^+$ T count ⩾100 cells/mm^3 and any HIV viral load. Patients were required to be on stable antiretroviral therapy (ART) or off ART for at least 4 weeks prior to the screening visit. Prior IFN-based treatment was defined as IFN-α monotherapy or IFN-α and RBV combination therapy administered for at least 12 weeks and discontinued for at least 4 weeks before the screening visit. Prior non-response was defined as a <2−$\log_{10}$ decrease in HCV RNA at week 12 or detectable HCV RNA at week 24 during HCV treatment. Prior relapse was defined as detectable HCV RNA after cessation of treatment in a patient who had undetectable HCV RNA at the end of treatment. A liver biopsy showing features consistent with chronic HCV infection was required within 18 months prior to study entry.

Exclusion criteria were decompensated liver disease (ascites, bleeding varices, or encephalopathy), other causes of liver disease (steatosis and steatohepatitis were not excluded), prothrombin time ⩾3 s, bilirubin > 20% above the ULN, albumin <3.0 g/dl, hemoglobin (Hb) ⩽11 g/dl, white blood cell count ⩽3000/mm^3, absolute neutrophil count ⩽1250/mm^3, platelet count ⩽70,000/mm^3, fasting blood glucose >115 mg/dl in non-diabetic patients, HbA1c > 8.5% in diabetic patients, serum creatinine ⩾1.5 mg/dl, abnormal TSH value, alpha-fetoprotein ⩾100 ng/ml, hemoglobinopathies, alcohol and/or drug abuse within 1 year of entry (active intravenous drug users were excluded), severe psychiatric disease, hypersensitivity to IFN or RBV, pregnancy or breastfeeding, and persons unwilling to use contraception during the study period.

Study design

Patients received 180 μg pegIFN-α-2a subcutaneously every week plus weight-based RBV (Pegasys® and Copegus®, Roche Laboratory, Nutley, NJ, USA), regardless of HCV genotype (800 mg/day for <65 kg; 1000 mg/day for ⩾65 kg and ⩽85 kg; 1200 mg/day for >85 kg). A complete medical history, physical examination, and laboratory tests were taken at the baseline visit. Additional data were collected at weeks 2, 4, 8, 12, 16, 20, 24, 36, and 48 during treatment and 24 weeks after the end of treatment. Unlike traditional treatment, patients who did not achieve a 2−$\log_{10}$ drop in HCV RNA at week 12 did not discontinue treatment. The decision to discontinue treatment was made at week 24 based on the week 20 HCV RNA result. Patients with a detectable HCV RNA level at week 20 were considered treatment failures and were diverted to a maintenance study arm to be discussed elsewhere. Patients with undetectable HCV RNA at week 20 were continued on treatment for a total of 48 weeks.

Partial early virological response (pEVR) was defined as a decrease of at least 2−$\log_{10}$ HCV RNA from baseline but with detectable HCV RNA at week 12. Complete EVR (cEVR) was defined as undetectable HCV RNA at week 12. End of treatment (EOT) response was defined as undetectable serum HCV RNA at week 48. Successful treatment was defined as sustained virological response (SVR) (an undetectable HCV RNA at 24 weeks after the end of treatment).

Safety and tolerability were assessed by the evaluation of adverse events, adherence, and discontinuation of study drugs at weeks 2, 4 and every 4 weeks through week 48 then at weeks 4, 12, and 24 after the end of treatment. For the management of side effects due to RBV, the initial dose was reduced to 600 mg daily until the event responsible for the dosage adjustment was resolved. For management of side effects due to pegIFN-α-2a, the initial dose was reduced by half until the event responsible for the dosage adjustment was resolved. Growth factors for anemia and neutropenia were used at the individual investigator's discretion.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The protocol and consent form were approved by a central institutional review board (IRB) and IRBs of participating sites. Informed consent was obtained from each patient included in the study.

Laboratory tests

Quantification of serum HCV RNA was performed using the AMPLICOR HCV MONITOR® Test, version 2.0 (Roche Molecular Diagnostics, Branford, CT, USA). The detection limit was 600 IU/ml. Quantification of serum HIV RNA was performed using the AMPLICOR® HIV-1 MONITOR UltraSensitive Test (Roche Molecular Diagnostics, Branford, CT, USA). The limit of detection was 48 copies/ml. To determine fasting serum levels of glucose and insulin, patients fasted overnight for at least 12 h prior to blood collection. Serum samples were let to stand for 15 min to allow clotting, centrifuged at full speed for 15 min, frozen in cryovials, and shipped the same day for analysis. Serum glucose was determined using the VITROS® 950 test (Ortho Clinical Diagnostics, Rochester, NY, USA) and insulin level was determined using the Immulite® 1000 assay (Siemens Healthcare Diagnostics Deerfield, IL, USA). All laboratory tests were performed at a central laboratory (Consolidated Laboratory Services Van Nuys, CA, USA).

The homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated using the equation described by Matthews et al.: HOMA-IR = fasting insulin (mU/ml) × fasting glucose (mmol/l)/22.5 [12]. Fasting glucose was measured in mg/dl and thus every value was multiplied by a factor of 0.055 before being used in the formula. A person with a HOMA-IR value above 2 was defined as having IR consistent with previous studies [13,14].

Liver pathology

Liver specimens, which were obtained 18 months prior to study entry, were fixed in formalin and embedded in paraffin before they were stained with hematoxylin–eosin and Masson Trichrome. Each was reviewed by a single pathologist at the central site (M-I F) who was unaware of the patient's clinical and biological data. The Ishak-modified histology activity index (HAI) classification scale was used to analyze the biopsy specimens for necroinflammation (range 0–12), and fibrosis (range 0–6). Cirrhosis was defined as a fibrosis score of 5–6 [15]. Steatosis was graded by percentage of liver parenchyma with fat-containing hepatocytes (0 for none; 1 for 1–32%; 2 for 33–67%; and 3 for >67% [16].

Statistical analysis

To determine the efficacy of the treatment, the percentage of patients achieving SVR was calculated. Consistent with previous studies on the efficacy of pegIFN and RBV, the denominator included all patients who received at least one dose of the study drug. Treatment failures included patients who were lost to follow up, discontinued treatment per study protocol at week 24, discontinued treatment due to adverse events, did not achieve SVR, withdrew from the study, or died.

To evaluate predictors of SVR, host characteristics (age, sex, race, body mass index (BMI), baseline HOMA-IR), HCV-related characteristics (HCV genotype, $\log_{10}$ HCV RNA, and non-response versus relapse to prior HCV therapy), HIV-related characteristics ($CD4^+$ T-cell count, HIV RNA, and current use of ART), and liver pathology (steatosis and cirrhosis) were evaluated. First, univariable analyses were done using Chi-square, Fisher's Exact test, Student's *t*-test or Mann–Whitney, as appropriate, with SVR as the outcome. Second, variables with *p*-value ⩽0.20 in univariable analysis were evaluated using forward and backward multivariable logistic regression to identify variables significantly associated with SVR.

To further study the relationship between IR and SVR, we conducted a post hoc matched, nested case–control analysis. Cases were those who achieved SVR and controls were those who did not. Cases and controls were placed into strata based on baseline HCV RNA and were matched on HCV genotype within each strata. McNemar's test was used for univariable analysis to identify significant

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Table 1. Baseline characteristics of the 96 HIV/HCV co-infected patients stratified by SVR and univariable analysis of predictors associated with SVR.

Parameter	SVR N (%)	No SVR N (%)	OR (95%CI)	*p*-value
Median age* (years)	46	49		0.15
(IQR)	(41-53)	(44-53)		
Sex				
Male	13 (93)	68 (83)	1	
Female	1 (7)	14 (17)	0.37 (0.05-3.09)	0.69
Race/ethnicity†				
Latino	5 (36)	35 (44)	1	
AA	3 (21)	25 (30)		
White	6 (43)	21 (26)	2.20 (0.68-7.01)	0.21
Median BMI (kg/m^2)*	26.4	25.7		0.77
(IQR)	(23.8-30.6)	(23.2-29.6)		
HCV Genotype				
1, 4	10 (72)	73 (89)	1	0.09
2, 3	4 (28)	9 (11)	3.24 (0.84-12.52)	
Median HCV RNA*(log_{10} IU/ml)	5.2x10^5	7.2x10^5		0.06
(IQR)	(2.1x10^5- 1.9x10^6)	(4.6x10^5-6.0x10^6)		
Prior HCV response				
Non responder	10 (71)	69 (84)	1	
Relapser	4 (29)	13 (16)	2.12 (0.58-7.81)	0.27
Median CD4$^+$ T-cells* (cells/mm^3)	630	525		0.14
(IQR)	(323-843)	(356-689)		
HIV RNA				
<48 copies/ml	9 (64)	58 (71)	1.34 (0.41-4.42)	0.75
Detectable	5 (36)	24 (29)	1	
On ART				
Yes	12 (86)	67 (82)	1.34 (0.27-6.64)	1.00
No	2 (14)	15 (18)	1	
ART regimen§				
PI-based	3 (25)	31 (46)	0.65 (0.19-2.27)	0.5
NNRTI-based	5 (41)	22 (33)	2.21 (0.63-7.69)	0.2
PI+NNRTI-based	2 (17)	4 (6)		
NRTIs only	2 (17)	10 (15)	0.68 (0.08-6.09)	1.00
Abacavir-containing ART				
Yes	2 (17)	21 (32)	0.44 (0.09-2.18)	0.49
No	12 (83)	61 (68)	1	
TDF-containing ART				
Yes	3 (25)	14 (22)	1.26 (0.30-5.29)	0.71
No	11 (75)	68 (78)	1	
Steatosis stage**				
0	8 (57)	35 (43)	1	
1	3 (22)	27 (33)		
2	2 (14)	9 (11)	0.56 (0.18-1.76)	0.32
3	1 (7)	11 (13)		
Cirrhosis				
Yes	1 (7)	25 (31)	0.18 (0.02-1.42)	0.10
No	13 (93)	57 (69)	1	
HAI score				
≥9	7 (50)	53 (64)	0.56 (0.18-1.75)	0.31
<9	7 (50)	29 (36)	1	
Diabetes				
Yes	1 (7)	7 (9)	0.82 (0.09-7.27)	1.00
No	13 (93)	75 (91)	1	
HOMA-IR				
≤ 2	6 (43)	11 (14)	1	
> 2	8 (57)	69 (86)	0.21 (0.06-0.73)	0.02

SVR, sustained virological response; HCV, hepatitis C virus; OR, odds ratio; AOR, adjusted odds ratio; IQR, interquartile range; AA, African American; BMI, body mass index; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhbitor; TDF, tenofovir disoproxil fumarate; HAI, histology activity index; HOMA-IR, homeostasis model of assessment of insulin resistance.
Data are *n* (%) unless otherwise indicated.
*Analyzed as a continuous variable.
**Steatosis analyzed as binary variable (steatosis ⩾1 vs no steatosis).
†Race/ethnicity analyzed as binary variable [White vs non-white (Latino and AA)].
§Denominator for percent calculation is patients taking ART.

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associations between SVR and possible predictors. Conditional logistic regression with SVR as the outcome was used to determine whether IR was a statistically significant predictor of SVR.

To determine if IR was correlated with steatosis and/or cirrhosis, Spearman's rank correlation was used. To determine the best predictor of SVR among these three, we used the multivariable logistic regression model obtained above with SVR as the outcome, all variables found to be statistically associated with SVR as covariates, and we substituted IR, steatosis, and cirrhosis as the main predictor. We compared the −2 log likelihood values for each model to identify which model had the best fit.

All analyses were done using SPSS Statistics 17.0 (Chicago, IL, USA) or Epi Info Version 6 (CDC, Atlanta, GA, USA). The Cox regression function was used for the conditional regression analysis. A p-value <0.05 (two-sided) was considered significant in all analyses.

Results

Baseline characteristics

Of the 102 patients enrolled, 6 did not receive study medication and 96 were included in the study (Table 1). Median age was 48 years (Interquartile range (IQR) = 44–53). The group was 84% male, 42% Latino, 29% African American, and 28% Caucasian. Of the 96 patients, 81 (85%) were infected with HCV genotype 1. Twenty-one (22%) patients had a past history of intravenous drug use and none were active users.

Of the 94 patients with available baseline fasting insulin and glucose levels, 77 (82%) had a HOMA-IR >2; 36 (38%) had a HOMA-IR between 2 and 4; and 41 (44%) had a HOMA-IR ⩾4. Steatosis was present in 53 (55%) of the liver biopsies and cirrhosis was present in 26 (27%). Of the 96 patients, 92 (96%) had a $CD4^+$ T-cell count ⩾200, 81 (84%) were on ART and 67 (70%) had undetectable HIV RNA.

Efficacy outcomes

Of the 96 patients who received at least one dose of the study drug, 37 (39%) experienced EVR. Twelve (13%) had pEVR and 25 (26%) had cEVR. An EOT response was achieved in 30 (31%) patients and SVR was achieved in 14 (15%) (Fig. 1). The negative predictive value of EVR to achieve SVR was 100%. The positive predictive value of EVR (partial and complete) to achieve SVR was 38%.

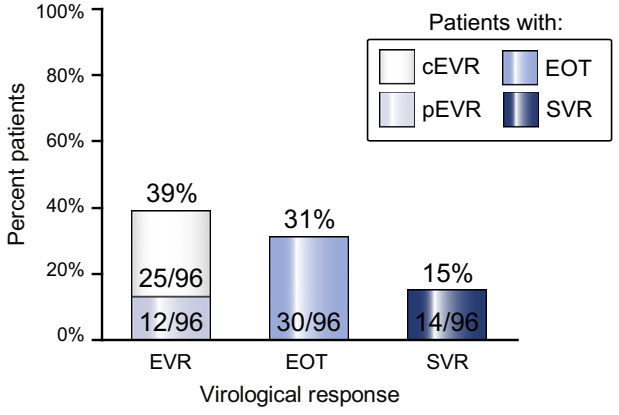

Fig. 1. Virological response of the 96 HIV/HCV co-infected patients. Percent of patients with cEVR, pEVR, and SVR. cEVR, complete early virological response; pEVR, partial early virological response; EOT, end of treatment; SVR, sustained virological response.

In the univariable analyses of possible predictors of SVR, IR was negatively associated with SVR [odds ratio (OR) 0.21; 95% CI 0.06–0.73, $p = 0.02$] (Table 1). In multivariable logistic regression, IR and baseline $\log_{10}$ HCV RNA were negatively associated with SVR [adjusted odds ratio (AOR) 0.17; 95% CI 0.05–0.64, $p = 0.009$, and AOR 0.36; 95% CI 0.14–0.93, $p = 0.04$, respectively]. The interaction between IR and HCV RNA was not significant.

A sub-analysis including only patients with HCV genotype 1 infection ($n = 81$) was performed. Out of 81 patients, 10 (12%) achieved SVR. In multivariable analysis, HOMA-IR >2 was the only independent negative predictor of SVR (AOR 0.16; 95% CI 0.04–0.67, $p = 0.01$). The African American race and Latino ethnicity were correlated with the presence of IR, but were not significant predictors of SVR when analyzed in the multivariable model.

Role of baseline IR and SVR

The matched, nested case–control analysis included 81 patients, with 14 cases matched to between 1 and 6 controls. In both univariable and multivariable analyses, IR was negatively associated with SVR (AOR 0.13; 95% CI 0.03–0.55, $p = 0.006$).

When looking at SVR in relation to the HOMA-IR score divided into 3 categories,<2, 2–4, and >4, there was a significant negative dose–response relationship between percent SVR and HOMA-IR: 35% (6/17) in HOMA-IR <2, 14% (5/36) in HOMA-IR between 2 and 4, and 7% (3/41) in HOMA-IR >4 ($p = 0.01$, chi-square test for trend) (Fig. 2).

Relationship between baseline IR and liver histology

IR was correlated with steatosis ($r = 0.22$, $p = 0.02$) and cirrhosis ($r = 0.23$, $p = 0.03$). Steatosis was present in 47/77 (61%) patients with IR, compared to 5/17 (29%) patients without IR ($p = 0.02$). Cirrhosis was present in 25/77 (32%) patients with IR, compared to 1/17 (6%) patients without IR ($p = 0.03$). When looking at the HOMA-IR score divided into 3 categories, <2, 2–4, and >4, there was a positive dose–response relationship between both percent

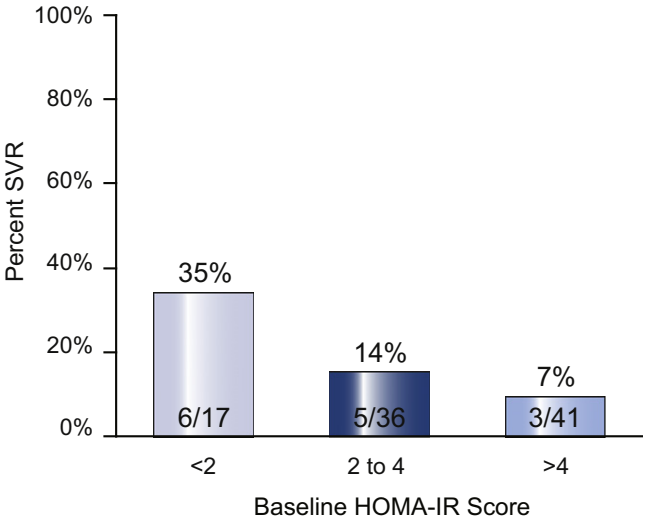

Fig. 2. Percent of patients achieving SVR stratified by baseline HOMA-IR score category (HOMA-IR < 2, 2–4 and >4). SVR, sustained virological response; HOMA-IR, homeostasis model of assessment of insulin resistance.

steatosis and HOMA-IR ($p = 0.02$, chi-square test for trend), and percent cirrhosis and HOMA-IR ($p = 0.03$, chi-square test for trend) (Fig. 3).

Using the multivariable logistic regression models with SVR as the outcome, $\log_{10}$ HCV RNA as a covariate, and steatosis or cirrhosis substituted in for IR, the models for steatosis and cirrhosis had larger −2 log likelihood values indicating that these models were less precise in predicting SVR (Table 2).

A sub-analysis including only patients without cirrhosis (n = 70) was performed. Out of 70 patients without cirrhosis, 13 (19%) achieved SVR. In multivariable analysis, HOMA-IR >2 was negatively associated with SVR (AOR 0.22; 95% CI 0.06–0.89, $p = 0.03$). Baseline $\log_{10}$ HCV RNA was also significantly associated with SVR (AOR 0.37; 95% CI 0.14–0.98, $p = 0.046$) in this analysis.

Safety and tolerability

The most common adverse events were cytopenias. Anemia with Hb <10 g/dl occurred in 13 (14%) patients and severe anemia (Hb <8.5) occurred in 3 (3%). A neutrophil count <750/mm^3 occurred in 74 (77%) and a neutrophil count <500/mm^3 occurred in 48 (50%). A platelet count < 50,000 cells/mm^3 occurred in 5 (5%) patients. RBV dose reduction was required in 18 (19%) patients during treatment, most frequently due to anemia. PegIFN-α-2a dose reduction was required in 25 patients (26%) during treatment, most frequently due to neutropenia. There were no incidents of opportunistic infections, episodes of hepatic decompensation, or development of HCC. There were two deaths in the study patients both of which were unrelated to study medications.

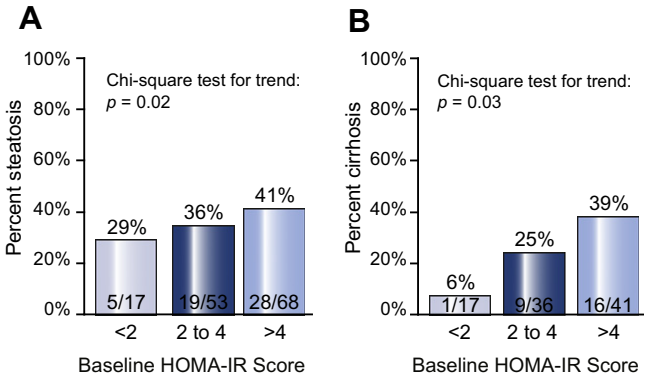

Fig. 3. Relationship between baseline HOMA-IR score category and liver histology. HOMA-IR; homeostasis model of assessment of insulin resistance.

Table 2. IR and correlated variables in the multiple logistic regression analysis*.

	SVR N (%)	No SVR N (%)	AOR (95%CI)	*p*-value	-2 log likelihood
IR	8 (57)	69 (86)	0.2 (0.06-0.73)	0.01	68.37
Steatosis	6 (43)	47 (57)	0.6 (0.18-1.76)	0.32	71.06
Cirrhosis	1 (7)	25 (31)	0.2 (0.02-1.42)	0.10	74.74

IR, insulin resistance (HOMA-IR >2); SVR, sustained virological response; AOR, adjusted odds ratio; *controlled for $\log_{10}$ HCV RNA.

Overall, 23 (24%) patients discontinued treatment. Thirteen discontinuations were due to adverse events. There were 8 discontinuations due to severe adverse events (SAEs), all within the first 24 weeks (3 severe anemia, 2 suicidal ideation, 1 hyperglycemia, 1 diarrhea and fever, and 1 rhabdomyolysis).

Discussion

This is the largest prospective study of HCV re-treatment in the population of HIV/HCV co-infected patients conducted so far. In this study, re-treatment with pegIFN-α-2a plus weight-based RBV led to a SVR rate of 15%. The strongest predictor of failure to achieve SVR was IR and the highest SVR rate of 35% was in patients with HOMA-IR <2. This is the first study to examine IR as a possible predictor of SVR during re-treatment of HIV/HCV co-infected patients. IR appears to predict SVR better than steatosis or cirrhosis. As such, these data provide important insight into the management of hepatitis C in co-infected persons who failed to respond to prior therapy.

Non-response to HCV treatment is common in HIV/HCV co-infected patients treated with pegIFN and RBV. Our population had a high prevalence of factors known to predict non-response to HCV treatment. Specifically, there was a high prevalence of men, African American race, Latino ethnicity, prior treatment non-responders as opposed to relapsers, HCV genotype 1 infection, high HCV RNA levels, steatosis, cirrhosis, and IR.

Baseline IR was strongly associated with virological response. These data are consistent with prior retrospective studies at the initial course of HCV treatment in co-infected patients. Among 238 co-infected patients treated with pegIFN-α-2b and RBV, Cacoub and colleagues reported that a HOMA-IR score > 2.5 was a negative predictor of SVR [17]. In a cohort of 134 co-infected patients, Ryan et al. similarly reported that a HOMA-IR score ⩾3.8 was a negative predictor of SVR [18]. A third retrospective study of 74 HIV/HCV co-infected patients reported that a HOMA-IR ⩾3.0 was a negative predictor of rapid virological response (RVR) [19]. RVR is achieved when serum HCV RNA is below the limit of detection at week 4 and is a known correlate of SVR [20]. One study found that IR was not associated with response to pegIFN (α-2a and α-2b) and RBV in treatment-naive HIV/HCV co-infected patients [21]. However the results appeared to show a negative dose–response relationship between baseline HOMA-IR score and SVR rate. These results may be explained by differences in patient samples, in terms of both sample size and patient characteristics. The patients in the study by Merchante et al. were younger (median age 40 vs 48 years), had lower BMI scores (median 22.9 vs 25.8), and were all Caucasians (100% vs 28% of our patients). Furthermore, they were HCV treatment naïve, had less advanced liver disease (15% cirrhosis vs 27% of our patients), and a lower prevalence of IR. Twenty-nine percent had HOMA-IR scores >4, compared to 44% in our population.

In our study, co-infected patients with HOMA-IR <2 had a SVR rate of 35% compared to 7–14% in those with higher scores. The 35% SVR rate in patients with HOMA-IR <2 is equivalent to SVR rates achieved in the HIV/HCV co-infected patients undergoing initial treatment. This suggests that calculation of HOMA-IR prior to treatment may improve the estimate of treatment response.

In HCV mono-infected patients, recent studies evaluated the impact of insulin sensitizing agents on SVR at the time of starting pegIFN and RBV treatment in patients with IR. Two showed posi-

tive results in defined populations [22,23], one did not [24]. An ongoing study using pioglitazone prior to pegIFN and RBV therapy is being conducted in HIV/HCV co-infected patients with IR who were non-responders to prior HCV treatment (ACTG 5239).

There is biological data supporting the association between IR and treatment response. Insulin diminishes the ability of IFN to inhibit HCV replication in a replicon model at insulin levels similar to those seen in patients with IR [25]. Elevated levels of suppressor of cytokine signaling 3 (SOCS3) in liver biopsies predict IFN treatment failure [26–28]. Some evidence suggests that SOCS3 down-regulates both insulin receptor substrate 1 (IRS-1), a key component of the insulin signaling pathway [29], and signal transducers and activators of transcription 1 (STAT1), a key component of IFN signaling [30]. This literature suggests that induction of SOCS3, which is reported to occur in cells carrying the HCV core gene [29,30], might contribute to both IR and IFN treatment failure in patients.

Our statistical models suggest that IR is more significantly associated with response to HCV re-treatment in HIV-infected patients than is steatosis or cirrhosis. Similar to previous studies, this study demonstrates a correlation between IR and both steatosis and cirrhosis [31,32]. Previous studies have found steatosis and cirrhosis to be negative predictors of response to HCV treatment in some patient populations [32–36]. The correlation between IR and steatosis/cirrhosis and their ability to negatively predict treatment response suggest all three may be markers of pathologic changes along a common pathway. With our current technology, IR is the only measure which does not require an invasive procedure and is therefore feasible for widespread use.

While we found baseline HCV RNA to be statistically associated with SVR, we did not find HCV genotype to be associated with SVR. This is not consistent with prior studies [10,11]. In the study by Labarga et al., HCV genotypes 2 and 3 infection was significantly associated with SVR compared to HCV genotypes 1 and 4, as was RBV plasma trough concentrations at week 4 [11]. The high prevalence of HCV genotype 1 compared to HCV genotypes 2 and 3 in this study may have prevented our ability to find associations. It is also possible that HCV genotype, while a significant predictor of treatment success for initial treatment of HIV/HCV co-infected patients, may not be as significant of a predictor during re-treatment. The low prevalence of patients with prior HCV relapse compared to HCV non-responders is also likely responsible for the lack of association with SVR in this study. However, prior small studies of re-treatment in the population of HIV/HCV co-infected patients have not found prior relapse vs non-response to be significantly associated with SVR [8,10,11].

Previous studies on predictors of SVR have often included EVR and total dose of pegIFN and/or RBV as predictors in their univariable and multivariable analyses; we did not. Because EVR almost always (98–100%) predicts SVR, EVR is likely along the causal pathway to SVR and therefore a measure of outcome not exposure. PegIFN-α-2a and weight-based RBV were given to all participants up to week 20 and virological status at week 20 determined further treatment. Thus, the total dose of pegIFN-α-2a and RBV was, in part, determined by the risk factors at baseline. Similar to EVR, medication dose in this study is a measure of outcome.

This study, with numerous strengths, expands the current literature but has some limitations. The most important strength is the prospective collection of data using standardized tools. Our study is limited by its sample size and the homogeneity of the patients in sex, age, and HCV genotype. The homogeneity of the population, especially the high prevalence of patients with HCV genotype 1 infection and HOMA-IR above 2, may have contributed to the strong relationship we found between baseline IR and SVR in this study. At the time the study was conducted, IL28B polymorphisms analyses were not performed. This information may have influenced our study results.

This study demonstrates that a proportion of HIV/HCV co-infected patients respond to HCV re-treatment. The best outcome is achieved in patients with baseline HOMA-IR $\leqslant$2. Calculating baseline HOMA-IR may be a useful tool when considering re-treatment. Future studies are needed to confirm these findings and determine if improvement of HOMA-IR prior to starting HCV therapy increases SVR rates. The impact of IR on SVR requires further study in patients receiving direct-acting antiviral agents as they are soon to become part of standard HCV treatment.

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