**Criteria Grid**
**Hepatitis C Research Studies, Tools, and Surveillance Systems**

| | |
|---|---|
| **Best Practice/Intervention:** | Eslam M. et al. (2011) The role of insulin resistance in HIV/hepatitis C virus-coinfected patients. *Current Opinion in HIV & AIDS*, 6(6):553-558 |
| **Date of Review:** | March 11, 2015 |
| **Reviewer(s):** | Christine Hu |

**Part A**

| | |
|---|---|
| ***Category:*** | **Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐<br>**Social Science** ☐ **Programmatic Review** ☒ |
| ***Best Practice/Intervention:*** | **Focus:** **Hepatitis C** ☐ **Hepatitis C/HIV** ☒ **Other:** **insulin resistance** _____<br>**Level:** **Group** ☒ **Individual** ☐ **Other:** _____<br>**Target Population:** **HCV/HIV co-infected patients**<br>**Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____<br>**Country of Origin:** **Spain**<br>**Language:** **English** ☒ **French** ☐ **Other:** _____ |

**Part B**

| | YES | NO | N/A | COMMENTS |
|---|---|---|---|---|
| *Is the best practice/intervention a meta-analysis or primary research?* | ☐ | ☐ | ☒ | Review; to summarize available data of insulin resistance in HCV/HIV co-infected patients and its effect on sustained virological response and disease progression |
| *Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?* | ☐ | ☒ | ☐ | |
| *Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?* | ☐ | ☒ | ☐ | Unclear methodology, though the findings could be extended to similar studies. |

| | | | | |
|---|---|---|---|---|
| *Are the best practices/methodology/results described applicable in developed countries?* | ☒ | ☐ | ☐ | Similar studies could be done. |
| | **YES** | **NO** | **N/A** | **COMMENTS** |
| *Are the best practices/methodology/results described applicable in developing countries?* | ☒ | ☐ | ☐ | |
| *The research study/tool/data dictionary is easily accessed/available electronically* | ☐ | ☒ | ☐ | Subscription to journal required for access |
| *Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say?* ***Please go to Comments section*** | ☐ | ☒ | ☐ | |
| *Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?* | ☐ | ☒ | ☐ | |
| *How is the research study/tool funded?* ***Please got to Comments section*** | ☐ | ☒ | ☐ | Study was not funded |
| *Is the best practice/intervention dependent on external funds?* | ☐ | ☒ | ☐ | |
| *Other relevant criteria:* _____ | ☐ | ☐ | ☐ | - Insulin resistance, when measure by HOMA-IR, seems to influence the possibility of achieving SVR in HCV/HIV co-infected patients receiving Peg-IFN and RBV |
| **WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW** | | | | |
| *Are these data regularly collected?* | ☐ | ☒ | ☐ | collected available data in the literature in the last 1 year |
| *Are these data regularly collected at and/or below a national level?* | ☐ | ☒ | ☐ | |
| *Are these data collected manually or electronically?* | ☐ | ☐ | ☒ | Unclear |
| **RESEARCH REPORTS** | | | | |
| *Has this research been published in a juried journal?* | ☒ | ☐ | ☐ | *Current Opinion in HIV & AIDS* |

| | | | | |
|---|---|---|---|---|
| *Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?* | ☐ | ☐ | ☐ | Utilize existing data/surveillance information |

# The role of insulin resistance in HIV/hepatitis C virus-coinfected patients

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**Purpose of review**

Insulin resistance, HIV, antiviral drugs and hepatitis C virus (HCV) infection contribute to a complex interaction involving the metabolic syndrome. The objective of this review was to explore the meaning of insulin resistance in HIV–HCV-coinfected patients and how it may impact on sustained virological response (SVR) and disease progression.

**Recent findings**

In the HIV/HCV coinfection setting, insulin resistance seems to be associated with a reduction in rapid virological response and SVR to pegylated interferon and ribavirin, both in naive and treatment experienced patients. A recent meta-analysis demonstrated insulin resistance impairs SVR rate with an odds ratio 0.47 (95% confidence interval 0.31–0.71). However, many confounding factors may promote contradictory results. Prevalence of insulin resistance depends on surrogate markers of insulin resistance and the threshold for defining impaired insulin sensitivity. For example, homeostasis model for the assessment of insulin resistance may be influenced by both methods of insulin measurement and interpretation. Insulin sensitizers, lifestyle changes and improvement in the use of protease inhibitors should be evaluated in the management of coinfected patients.

**Summary**

Insulin resistance is common finding in patients with HIV/HCV coinfection, with wide clinical consequences including progression of hepatic fibrosis and reduction in the response to antiviral treatment. Our understanding of this relationship continues to improve. More prospective studies are required to improve future management.

**Keywords**

HIV/HCV coinfection, insulin resistance, liver fibrosis, sustained virological response

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## Introduction

Due to shared routes of transmission, approximately 15–30% of HIV-infected persons in the USA and Europe are also infected with hepatitis C virus (HCV) [1,2]. HCV core protein promotes insulin resistance inducing degradation of insulin receptor substrate (IRS)-1. Moreover, in patients with HIV infection, the virus itself and highly active antiretroviral therapy promotes insulin resistance and metabolic syndrome [3,4]. The prevalence of insulin resistance in HIV-infected patients is estimated to affect more than a third of individuals, despite a lower BMI than the general population. Both insulin resistance and HIV infection have been shown to worsen fibrosis progression [5,6]. In hepatitis C monoinfection, insulin resistance has been found to be associated with both fibrosis progression and impaired sustained virological response (SVR) rate [7••]. However, in coinfected patients insulin resistance has not been found to be associated with either fibrosis progression or steatosis development [8] and its association with SVR has been controversial. We, therefore, conducted a meta-analysis to analyze the overall impact of insulin resistance on SVR in coinfected patients. Some of the controversial data in insulin resistance, fibrosis progression and SVR may be associated with limitations in the measurement of insulin and interpretation of homeostasis model for the assessment of IR (HOMA-IR). In this review, we summarize the available data in the literature in the last 1 year.

## Definition and diagnosis of insulin resistance

HOMA-IR as a surrogate marker of insulin resistance, insulin is a key regulator of glucose homeostasis. Insulin resistance has been described as a condition in which a greater than normal amount of insulin is required to obtain a quantitatively normal glucose response [9]. Insulin resistance leads to impaired glucose tolerance and plays an important pathophysiological role in the development of type 2 diabetes mellitus (T2DM) [10]. Insulin resistance can be evaluated by direct measurement of insulin-mediated glucose uptake or, alternatively, by a surrogate

estimation of insulin resistance. The HOMA model has proved to be a robust clinical and epidemiological tool for the assessment of insulin resistance and was originally developed by Matthews *et al.* [11] as a simplified surrogate marker to measure insulin resistance [12]. This model has been widely used to-date in most human studies. Many concerns exist around determination of insulin resistance including methods of measurement of insulin, handling of blood samples, the conversion factor between SI units and μU/ml, the formula to calculate HOMA-IR and the threshold to define insulin resistance. Insulin assays are not standardized and are not comparable between studies. Insulin inter-assay variations can be large, and values have varied considerably between different laboratories [12,13]; careful handling of the blood samples is essential because hemolysis results in the degradation of insulin, whereas freezing the samples results in the degradation of C-peptide and glucose, with false-negative results being one of the consequences. Additionally, insulin should be reported in International Units (SI), but the conversion factor from pmol/l to SI units is not uniform among manufacturers [14]. HOMA-IR itself can be calculated using the formula from Matthews *et al.* [11] or using the HOMA-2 calculator (available at http://www.dtu.ox.ac.uk/homacalculator/). However, results from both methods are quite different resulting in bias in comparative studies; insulin secretion is pulsatile [15]; and finally, there is no international consensus regarding the threshold that defines insulin resistance by using HOMA-IR. Generally, a HOMA-IR greater than 4 has been accepted as indicative of insulin resistance [16]. Taking into account all these limitations, HOMA-IR remains the most widely accepted indicator of insulin resistance in HIV–HCV-coinfected patients.

## Insulin resistance in HIV/hepatitis C virus coinfection: prevalence and associations

Insulin resistance is present in around 30% of individuals with HIV/HCV-coinfected patients [17]. In HIV-infected patients, the incidence of T2DM is four times higher than in HIV-negative persons [18], and insulin resistance is recognized in 50% of protease inhibitor-treated patients [19]. Pathogenesis of insulin resistance is multifactorial in HIV/HCV-coinfected people (Fig. 1), including drugs and virus infections. In-vitro, animal models, and healthy human volunteer studies have greatly assisted efforts to understand the contribution of individual protease inhibitors to the emergence of insulin resistance and/or overt diabetes mellitus in patients receiving protease inhibitors as part of highly active anti-retroviral therapy (HAART). The first studies to establish that protease inhibitors (specifically indinavir, ritonavir and amprenavir) are capable of acutely inducing insulin resistance were performed in cultured 3T3-L1 adipocytes and *Xenopus oocytes* in which glucose transporter (GLUT)4 was identified as a direct target of indinavir [20]. Protease inhibitors impaired intracellular insulin signaling, mainly degradation of IRS-1 [21] and AKT [22], a finding that has been observed most frequently following chronic drug exposure as opposed to acute exposure, which produces impaired glucose uptake by GLUT4 inactivation [13]. The lack of glucose intake is mediated directly by HCV through inhibition of IRS1-2 and by the increase of suppressor of cytokines signaling-3 and indirectly by both HIV and HCV through increased cytokine levels (tumor necrosis factor α and interleukin-6) [23]. In addition, the lack of βoxidation due to HCV, peroxisome proliferator activation receptor α and γ, inhibition by HCV, steroyl and carbohydrate regulatory binding protein (SREBP and ChreBP) activation by antiretroviral medications (ART) [15].

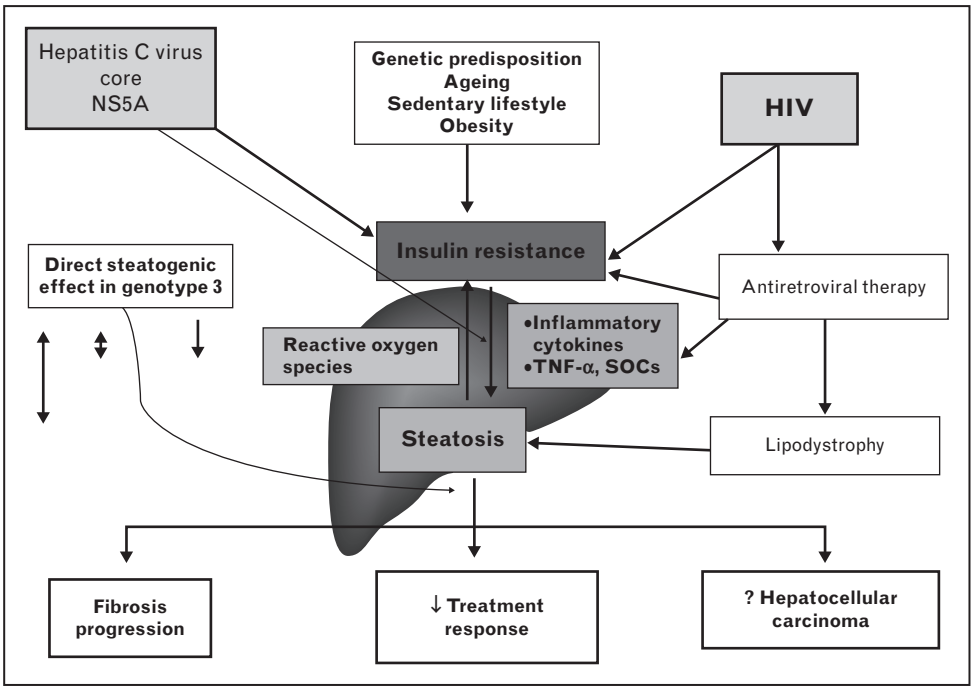
**Key points**

- Insulin resistance in setting of HCV/HIV coinfection is a multifactorial and common finding.
- Our understandings of the pathogenesis of HCV/HIV coinfection-induced insulin resistance and its deleterious effects are greatly improved.
- The impact of insulin resistance on the natural history of the disease has not been completely confirmed and need further studies.
- A meta-analysis confirms an association between insulin resistance and impaired sustained virological response (SVR).
- Insulin-sensitizing agents including the thiazolidinediones, metformin and statins have a variable and unconfirmed response on viral kinetics and SVR.

## Impact of insulin resistance on the natural history of HIV/hepatitis C virus coinfection

Several (Fig. 1) reports have found that hepatic steatosis is common in patients with HIV/HCV coinfection [24] and greater than expected from the general population. However, steatosis does not correlate with the characteristics of HIV infection (such as AIDS status, CD4 cell count and HIV viral load) [25], and moreover, no correlation has been seen with HAART [26]. Measurement and interpretation of HOMA-IR, colinearity between HOMA-IR and variables associated with metabolic derangements, and the characteristics of the cohort under study seem to influence the interaction between insulin resistance and fibrosis progression. Earlier studies failed to find an association between insulin resistance and fibrosis progression in patients with HIV/HCV coinfection. In a retrospective study, carried out in 79 patients coinfected with HIV/HCV and who underwent a liver biopsy, no association was elucidated between insulin resistance and advanced fibrosis [27]. These findings were confirmed in 170 HIV/HCV coinfected patients matched by age, sex and genotype with 170 HCV

**Figure 1 Hepatitis C virus, HIV, antiviral therapy and genetic and environmental factors promoted insulin resistance in coinfected patients, affecting the possibility of achieving sustained virological response**




The impact on natural history of the disease has not completely confirmed. SOCs, suppressor of cytokine signalling; TNF, tumor necrosis factor.

monoinfected. Insulin resistance was associated with steatosis and fibrosis progression in monoinfected, but not in HIV/HCV-coinfected patients [8]. However, a further study from the same group, assessing liver fibrosis by transient elastography, demonstrated that insulin resistance was independently associated with fibrosis progression [28]. An explanation is not yet available. Hepatocyte steatosis could influence elastography resulting in a false-positive diagnosis of advanced fibrosis [29•]. In 110 patients, the rate of false positive (F3 instead of F2) was 25% in patients with steatosis. Thus, together with obesity and alanine aminotransferase flares, steatosis should be kept in mind when measuring stiffness by transient elastography and may have influenced previous results.

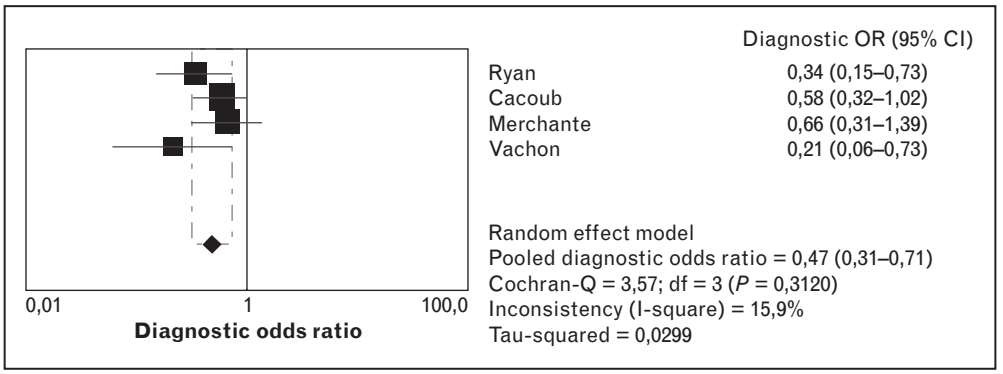
## Impact of insulin resistance on treatment response

As with the impact of insulin resistance on natural history, emerging data from several recent studies have yielded conflicting results about the association between insulin resistance and treatment response [rapid virological response (RVR) and SVR] in HIV/HCV-coinfected patients treated with peginterferon and ribavirin. Nasta *et al.* [30] found that insulin resistance is an important factor associated with reduced RVR in HIV/HCV-coinfected patients. These findings were confirmed in a cohort of 238 coinfected French patients and 218 HIV/HCV-coinfected Spanish people. Increased HOMA-IR was associated with a reduced SVR rate and was the strongest predictor of non-SVR [31]. However, Merchante *et al.* [32] demonstrated in a retrospective study that HOMA was not a significant predictor of SVR to pegylated (Peg) interferon (IFN)/ribavirin (RBV) in a cohort of 155 patients. This study identified HCV genotype, viral load and baseline Low-density lipoprotein cholesterol (LDL-C) levels instead as independent predictors of SVR. Lastly, in IFN-experienced patients without insulin resistance were significantly more likely to achieve SVR [33••]. Six out of 17 patients (35%) with a HOMA less than 2 achieved SVR, whereas eight out of 77 patients (10%) with HOMA more than 2 [odds ratio (OR) 0.21; 95% confidence interval (CI) 0.06–0.73; $P < 0.02$]. In a meta-analysis including 623 coinfected patients treated with peginterferon and ribavirin and analyzing insulin resistance (defined as HOMA-IR more than 2 to HOMA-IR more than 4) from these four studies [9,30–32,33••,34] (Fig. 2), an association between insulin resistance and impaired SVR was demonstrated [OR 0.47 (95% CI 0.31–0.71)]. SVR rate decreased to a half in patients with altered HOMA-IR (Table 1) [16,31,32,33••,34].

## Management of insulin resistance in HIV/HCV-coinfected individuals

A recent meta-analysis showed that metformin is the best insulin sensitizer to demonstrate beneficial effects on all

**Figure 2 Forest plot showing a meta-analysis analyzing the impact of insulin resistance on sustained virological response**




Pooled data of 623 patients included in four studies.

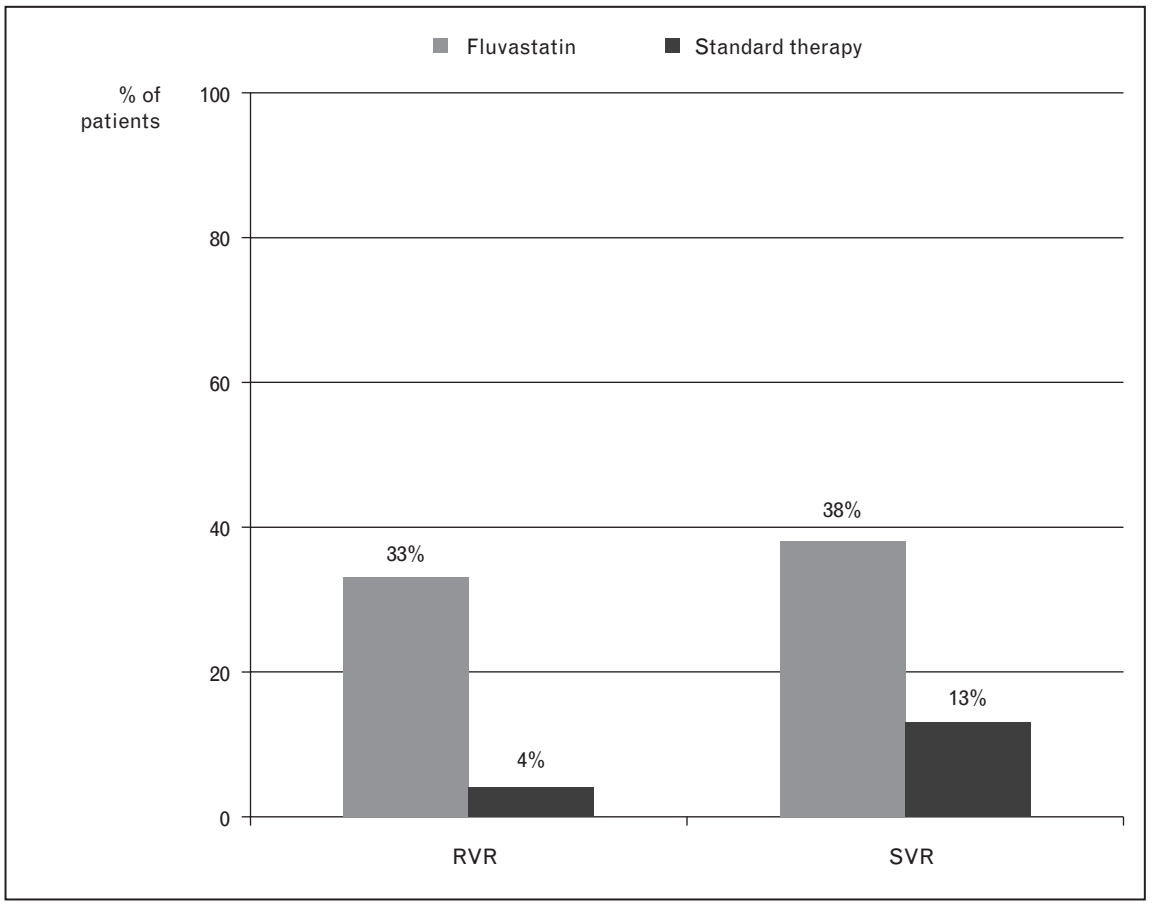
components of HIV-associated lipodystrophy syndrome, whereas pioglitazone may be safer, but with smaller benefits [35]. Pooled data involving 920 patients demonstrated that rosiglitazone modestly improved fasting insulin but worsened triglycerides, LDL and High-density lipoprotein cholesterol (HDL). Conversely, pioglitazone had no impact on fasting insulin, triglycerides or LDL but improved HDL. Metformin reduced fasting insulin, triglycerides, BMI and waist-to-hip ratio. Adding metformin to Peg-IFN/RBV in 123 Spanish patients with hepatitis C genotype 1 slightly improved SVR from 42 to 52%. In the subgroup of women, SVR rate was twice in women receiving metformin, reaching statistically significant differences [36]. The usefulness of metformin in the management of coinfected patients with genotype 1 should be tested, as improving insulin sensitivity might be a useful adjunct to HCV therapy in HIV–HCV-coinfected patients. Recently, Georgescu *et al.* [37] in a randomized trial analyzed the impact of adding 20 mg/day of fluvastatin or placebo to peginterferon and ribavirin on SVR in a cohort of 209 chronic hepatitis C genotype 1 patients irrespective of baseline lipid profile. Fluvastatin slightly increased sustained response rate in comparison with placebo [66 of 104 (63%) vs. 52 of 105 (50%); $P = 0.05$]. Accumulating in-vitro observations suggesting that statins may inhibit viral replication [38,39] have prompted further assessment of the potential value of statins *in vivo*. In a large retrospective analysis of the Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy trial, which assessed the optimal pegylated interferon therapy and enrolled 3070 genotype 1 chronic hepatitis C patients, Harrison *et al.* [40••] showed that the use of statins was associated with a significantly increased rate of SVR. Interestingly, this effect was noticed to be independent of the baseline lipid profile. Statin users had higher chances of SVR when aged more than 48 years, of non-African-American ethnicity and woman. Collaborative retrospective data was noted in a very large cohort of diabetic Chronic hepatitis C patients (1704 patients from the 8293 patients identified in the study), in which use of statin was independently associated with improved SVR [41••]. In HIV/HCV-coinfected patients, Milazzo *et al.* [42] initially reported disappointing results in a pilot trial enrolling 42 HCV/HIV patients treated with fluvastatin 80 mg daily, in whom the expected decrease of serum cholesterol and LDL was paralleled by a paradoxical increase in HCV RNA levels. However, in a further randomized trial involving 44 patients with HIV/HCV genotype 1 coinfected fluvastatin addition (80 mg/day) to

**Table 1 HCV/HIV associated insulin resistance/diabetes and sustained virological response**

| Author | Year | HOMA cutoff | Number | % of patients with IR | SVR in IS (%) | Non-SVR in IS (%) | SVR in IR (%) | Non-SVR in IR (%) | Odds ratio; 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| Ryan *et al.* [31] | 2010 | >3.8 | 134 | 31 | 54 | 39 | 13 | 28 | 0.33; 95% CI: 0.15–0.72; $P = 0.006$ |
| Cacoub *et al.* [17] | 2009 | >2.5 | 238 | 32 | 72 | 90 | 24 | 52 | 0.58; 95%CI: 0.32–1.02; $P = 0.05$ |
| Merchante *et al.* [32] | 2009 | >4 | 155 | 29 | 42 | 68 | 13 | 32 | 0.66;95%CI: 0.31–1.39); $P = 0.28$ |
| Donato *et al.* [34] | 2010 | >2.6 | 86 | NA | NA | NA | NA | NA | 0.77; 95%CI: 0.27–2.22; $P = 0.674$ |
| Vachon *et al.* [33••] | 2011 | >2 | 96 | 80 | 6 | 11 | 8 | 69 | 0.21; 95%CI: 0.06–0.73; $P = 0.02$ |

CI, confidence interval; IR, insulin resistance, IS, international units; SVR, sustained virological response.

**Figure 3 Response rate by intent-to-treat analysis**




RVR, rapid virological response at week 4; SVR, sustained virological response at week 24 after cessation of therapy. Reproduced with permission from [44].

SOC therapy significantly improved RVR, although it did not significantly increase SVR rate [43] (Fig. 3) [44].

As an alternative or adjunct to pharmacological improvement of insulin resistance, assessment of the effect of a dietary and/or lifestyle changes on insulin resistance in coinfected patients, with its impact on hindering the progression of liver fibrosis and enhancing response to antiviral treatment, is interesting and worthy of further evaluation, considering that weight loss can improve liver fibrosis in HCV-monoinfected persons [44].

## Conclusion

Insulin resistance is a multifactorial and common finding in patients with HIV/HCV coinfection that may have clinical consequences. Insulin resistance measured by HOMA-IR seems to influence the possibility of achieving SVR in coinfected patients receiving standard of care Peg-IFN and ribavirin. However, the impact of baseline factors on SVR may change when new Directly Acting Antiviral agents for HCV are available, as by improving the SVR rate, the predictive role of baseline factors is likely to fall. Nevertheless, the interaction between HAART, both viruses, genetic and environmental factors should be addressed in further studies to clarify the main mechanism of interaction and whether therapeutic options focusing on the management of insulin resistance may improve both the natural history and SVR rates in coinfected patients.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 570).

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