Received: 1 October 2017 | First decision: 30 October 2017 | Accepted: 7 January 2018

DOI: 10.1111/apt.14538

WILEY AP&T Alimentary Pharmacology & Therapeutics

# The adverse effects of interferon-free regimens in 149 816 chronic hepatitis C treated Egyptian patients

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## Summary

**Background:** Interferon-free regimens are associated with high sustained virological response; however, associated adverse effects have yet to be fully reported.

**Aim:** To evaluate the adverse effects associated with the different direct-acting antiviral drug (DAA) regimens in Egyptian patients.

**Methods:** This multicenter retrospective study included all adverse effects during and after treatment with DAA regimens of 149 816 chronic hepatitis C treated Egyptian patients. Patients received sofosbuvir (SOF)/ribavirin (RBV) (n = 21 835), SOF/simeprevir (n = 24 215) SOF/daclatasvir (DCV) (n = 58 477), SOF/DCV/RBV (n = 45 188) and paritaprevir/ombitasvir/ritonavir/RBV (n = 101). The duration of treatment varied between 12 and 24 weeks. All changes in the treatment regimens, discontinuation, mortality, and serious side effects were reported.

**Results:** Adverse effects developed in 2475 (1.7%) (mean age [54 ± 9], male gender [53%]) patients. Serious side effects developed in 68% of these patients, and SOF/RBV was the most common causing regimen (73%, $P < 0.001$). Anaemia and hyperbilirubinemia were the most common side effects (731/149816, 0.5% and 463/149816, 0.3%, respectively) and SOF/RBV (588/21835, 3% and 353/21835, 1.6%, respectively) showed the highest incidence in the treated patients. Hepatocellular carcinoma and mortality were reported in 0.02% and 0.06% of all treated patients, respectively. Patients with liver cirrhosis showed higher incidence of serious side effects (Log rank $P = 0.045$) and mortality (Log rank $P = 0.025$) than patients without liver cirrhosis. Male gender ($P = 0.012$), lower haemoglobin ($P < 0.001$), platelets ($P < 0.001$) and albumin ($P = 0.001$), higher bilirubin ($P = 0.002$) and cirrhosis ($P < 0.001$) were factors associated with serious side effects development.

**Conclusion:** Adverse effects associated with DAAs are few, anaemia being the most common. SOF/RBV regimen showed the highest rate of side effects while SOF/DCV showed the least.

The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

## 1 | INTRODUCTION

Hepatitis C virus (HCV) remains a global burden worldwide and the leading cause of liver cirrhosis with its associated complications including hepatic decompensation and hepatocellular carcinoma (HCC),[1,2] The worldwide seropositivity is around 115 million (1.6%), with actual viremic patients at around 71 million (1%) (range 62-79 million).[1,3] Egypt is one of the highest endemic seropositive areas worldwide (>5%) with respect to the adult population.[4] The implementation of the combined PEGylated interferon and ribavirin regimen (PEG-IFN/RBV) in the standard of care for chronic HCV-infected Egyptian patients of genotype 4 was associated with a limited sustained virological response (SVR), reaching a maximum of 60%.[5] The launch of the National Treatment Programme of chronic HCV with direct-acting antiviral drugs (DAAs) improved the SVR to higher levels using different DAAs; SVR reached 96% in sofosbuvir (SOF)/PEG-IFN/RBV,[6] (78%-98%) in SOF/ribavirin (SOF/RBV),[7] in SOF/simeprevir (SOF/SIM) (94%-100%)[5,8-10] in SOF/daclatasvir (SOF/DCV) reached (95.1%),[11] in SOF/ledipasvir (SOF/LED) reached (87%-97%)[12] and in paritaprevir/ombitasvir/ritonavir/ribavirin (PTV/OBV/r/RBV) (94%-97%).[13] The list of adverse effects secondary to PEG-INF/RBV combination is long, in addition to the limitation of this regimen in decompensated cirrhosis and other patients. The use of DAAs in all age groups and even in patients with decompensated liver cirrhosis as well as those with renal diseases has increased the incidence of adverse side effects development. The adverse effects of DAAs have not been thoroughly discussed. Identification of the adverse effects in the different DAA regimens, particularly in those with advanced liver cirrhosis will help in improving the selection of patients who will benefit from each regimen and decrease the incidence of decompensation and risk of complications. Thus, the aim of this study was to evaluate the adverse effects associated with different DDA regimens in Egyptian patients.

## 2 | PATIENTS AND METHODS

### 2.1 | Study cohort

This study was conducted in compliance with the Helsinki Declaration. Approval of the National Committee of Viral Hepatitis (NCCVH) was given. Data were collected from the National Network of the Treatment Centre from 19 centres from Upper and Delta Egypt. 149 816 chronic HCV patients received different DAA drug regimens through the National treatment programme of Hepatitis C in Egypt between September 2014 and September 2016. In total, 2475 patients (1.7%) developed adverse effects during and after treatment with DAAs and were included in this study. Figure 1 shows the flow diagram of the treatment regimens, illustrating patients who developed adverse effects according to each regimen and treatment response. Death occurred in 85 patients (3.4%) during treatment, due to various causes (mostly hepatic decompensation); three of them died due to diabetic comas, some reported deaths of unknown aetiologies. Forty-six patients reached SVR24 and three patients were relapsers, while 39 patients died before SVR24. SVR24 was not reported in n = 879/2475 patients with side effects. Patients were further classified according to the presence (n = 1689) and absence (n = 786) of serious adverse effects. The latter effects are defined as the new onset of hepatic encephalopathy, new onset and progressive ascites, progressive jaundice, hepatic decompensation (bilirubin >3 mg/dL, albumin <2.8 g/dL, international normalisation ratio [INR] >1.7), new onset variceal bleeding, anaemia with haemoglobin (HB) <10 g/dL not responding to haematopoitic agents and/or associated with clinical manifestations. Hospital-acquired admission due to another organ decompensation (cardiac, pulmonary, renal), severe activation of extrahepatic manifestations, development of HCC, uncontrolled of previously controlled diabetes mellitus and occurrence of diabetic coma formed another category for analysis.

### 2.2 | Treatment regimens

Inclusion criteria were according to Egyptian guidelines of HCV treatment (NCCVH). Between September 2014 and November 2015, inclusion criteria were as follows: patients with F3, F4, body mass index (BMI) ≤35, age 18-70, platelets $\leq 30 \times 10^3/\mu L$, bilirubin ≤5 mg/dL, haemoglobin ≥10 g/dL, post-liver transplantation ≥F2, post-kidney transplantation ≥F2 and extrahepatic vasculitic syndromes with any fibrosis stage, HCC after 12 weeks intervention free, controlled ascites and small non-risky varices, interferon-experienced after 24 weeks of treatment. Guidelines were updated in November 2015 and included, age between 18 and 75, any BMI, all fibrosis stages, HCV RNA positive, naïve, and experienced patients. Patients were categorised into two groups; easy-to-treat group; treatment naïve, total bilirubin ≤1.2 mg/dL, albumin ≥3.5 g/dL, INR ≤1.2, platelet count $\geq 150 \times 10^3/\mu L$ and were treated for SOF/DCV for 12 weeks and difficult-to-treat group; PEG-IFN experienced, SOF/RBV failure bilirubin ≥1.2 mg/dL, albumin ≤3.5 g/dL, INR ≥1.2 and/or platelets $<150 \times 10^3/\mu L$ and were treated with SOF/DCV/RBV for 24 weeks. Patients were excluded from the treatment if bilirubin >3 mg/dL, albumin <2.8 g/dL, INR ≥1.7, platelet count $<50 \times 10^3/\mu L$, HCC except after 4 weeks' intervention free of malignancy. Extrahepatic malignancy except after 2 years malignancy-free interval, pregnancy, and lactation, HbA1c >9%. During the period between September 2014 and February 2015, patients were treated with SOF (400 mg)/RBV regimen for 12 weeks/24 weeks (n = 21 835), (RBV <75 kg 1000 mg/day and ≥75 kg 1200 mg/day with starting dose 600 mg in two divided doses), and SOF/SIM (150 mg) regimen for 12 weeks (n = 24 215). After February 2015, easy-to-treat patients received SOF/DCV for 12 weeks' regimen (n = 58 477) and the difficult-to-treat group and relapsers of SOF-containing regimens received SOF/DCV/RBV (n = 45 188) for 24 weeks. Ritonavir-boosted paritaprevir/ombitasvir/RBV (PTV/OBV/r/RBV) for 12 weeks (n = 101), which is a regimen indicated for renal patients.

### 2.3 | Treatment response

Success of treatment was evaluated as SVR at week 12 post treatment (SVR12) (for 12 weeks' treatment) and week 24 post

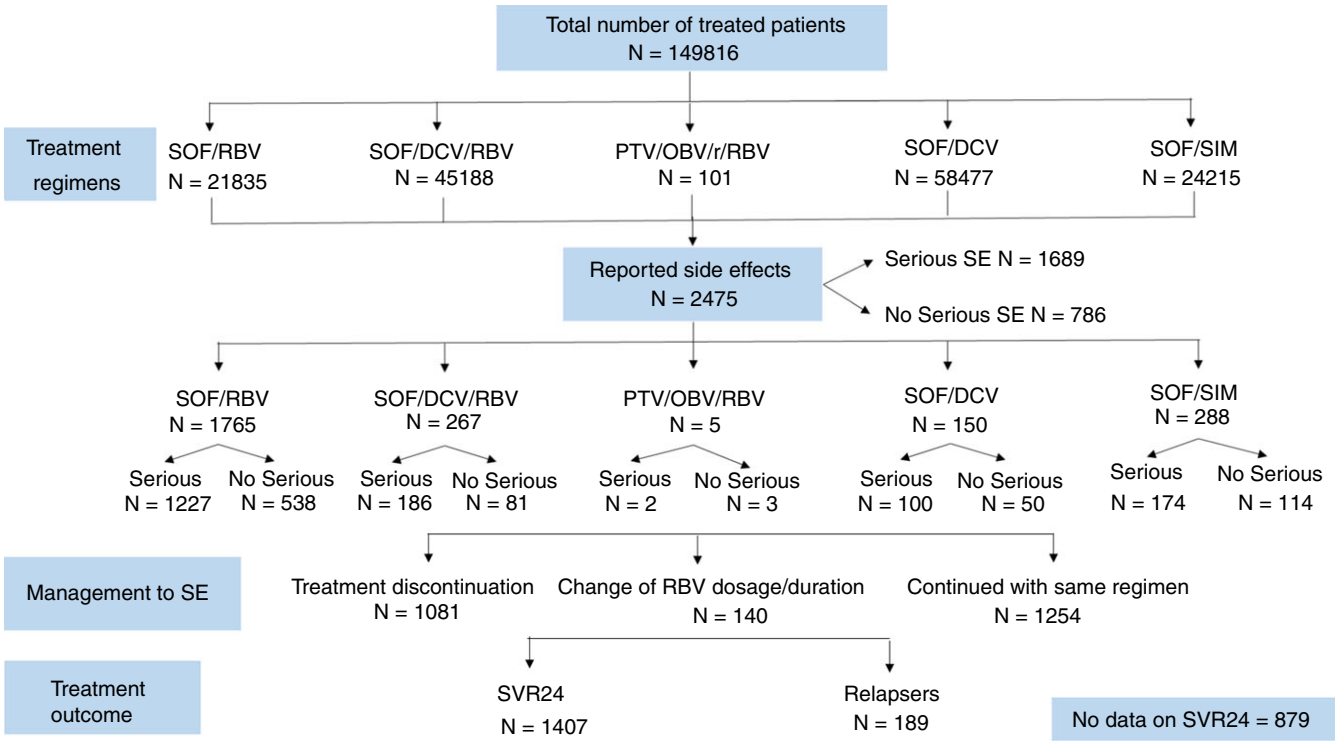



**FIGURE 1** Diagram describing DAA treatment regimen distribution, related side effects, management of side effects and treatment outcome. N, number; SOF/RBV, sofosbuvir/ribavirin; SOF/DCV, sofosbuvir/daclatasvir; PTV/OBV/r/RBV, paritaprevir/ombitasvir/ritonavir/ribavirin; SOF/SIM, sofosbuvir/simeprevir; SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin; SE, side effects; SVR 24, sustained virological response 24 weeks after treatment

treatment (SVR24; for those treated for 24 weeks). SVR is defined as undetected RNA by a sensitive quantification technique. Those with HCV RNA reappearance any time during and after treatment were termed relapsers.

## 2.4 | Clinical measurements

Before treatment, demographic, clinical adverse events were recorded. During and after treatment, all adverse events were recorded with clinical decompensation which included coma and death at week 4 (W4), week 12 (W12) during treatment (for SVR12) and week 16 (W16), week 20 (W20) and week 24 (W24) (for SVR24), W4 and W24 post treatment for both. Liver cirrhosis was diagnosed before treatment with liver biopsy when present, or the combination of two or more of the clinical, laboratory or imaging techniques; Fib-4 > 3.25,[14] transient elastography >17.5 kPa,[15] and the presence of oesophageal varices and platelet count $<140 \times 10^3$ μm/L.

## 2.5 | Laboratory measurements

Before treatment, routine laboratory data including alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, albumin, INR, prothrombin concentration, HB, total leucocytic count (TLC) and neutophilic count (ANC), platelet count, random blood sugar with HbA1c, alpha-fetoprotein, creatinine, HBsAg, HCV RNA were taken. During follow-up AST, ALT, bilirubin, HB, TLC with ANC, platelet count and creatinine were assessed at W4, W12 during treatment (for SVR12) and W16, W20 and W24 (for SVR24). Quantitative HCV RNA was assessed at W4 and W24 post treatment for both.

## 2.6 | Abdominal ultrasonography

Abdominal sonographic examinations were performed before treatment for the presence of liver cirrhosis signs; surface irregularity, hepatic irregularity, increased angle of lower border >45° and signs of portal hypertension splenomegaly (longitudinal diameter >13 cm), portal vein diameter >12 mm, splenic and superior mesenteric >6 mm, presence of collaterals, and presence of ascites. For exclusion of HCC, for those with suspected focal lesions, dynamic triphasic CT was recommended to exclude malignancy before treatment start.

## 2.7 | Statistical analysis

SPSS software was used for statistical analysis (version 22, SPSS, Chicago, IL). Values were expressed as means with their SD. The Mann-Whitney test was used for comparisons between two independent variables, while the Wilcoxon test was used to compare independent related variables. Univariate and multivariate analyses using binary logistic regression analysis to detect the predictors of serious side effects development in all patients and in each treatment separately as well as predictors of HCC occurrence. The incidence of side effects and death occurrence in patients with and without liver

cirrhosis was calculated using the Kaplan-Meier curves and log rank comparative tests. Any *P*-values less than 0.05 were considered statistically significant.

## 3 | RESULTS

### 3.1 | Characteristics of the study cohort

In this retrospective multicenter study, 149 816 HCV chronic infected Egyptian patients were treated with different regimens of DAAs. Adverse effects developed in 2475 patients (1.7%) mean age (54 ± 9) male gender (n = 1322/2475) patients (53%), and mean BMI (30 ± 5 kg/m$^2$). Naïve patients were (87%) and liver cirrhosis was confirmed pre-treatment in (n = 1999) patients (81%) with Child A was calculated in (80%) and Child B in (20%). Baseline characteristics of patients who developed adverse effects are stated according to the treatment regimens in (Table 1). Adverse events were reported in 5 patients out of 101 who received PTV/OBV/r/RBV regimen, mean age was (61 ± 5 years old), three patients were males and one patient had liver cirrhosis. Serious side effects were reported in (n = 1689) patients (68%). In that group of patients, treatment discontinuation was decided in (n = 641/1689) patients (38%); the regimen changed in (n = 129/1689) patients (8%), and was continued in (n = 869/1689) patients (n = 52%). Haematological side effects developed in (n = 783/1689) patients (46%), of which anaemia accounted for (n = 731/783) (93%). Hepatobiliary complications were observed in (n = 757/1689) patients (45%) of which hyperbilirubinemia developed in (n = 463/757) patients (61%). HCC was detected in (n = 33/2475) of patients with side effects (1.3%).

### 3.2 | Efficacy of DAAs in patients with adverse events

A total of 1642/2475 patients with side effects reached SVR24. The overall SVR24 was detected in n = 1450/1642 patients (88%), 43 of those died, mostly due to hepatic decompensation. Relapse was observed in n = 192/1642 patients (12%), and three patients of those died secondary to hepatic decompensation. SVR24 data were lost in 879/2475 patients, of those 39 patients died before reaching SVR24. SVR24 in SOF/RBV was 89%, SOF/SIM was 87%, SOF/DCV was 90%, SOF/DCV/RBV was 86%.

### 3.3 | Adverse effects according to drug regimens

Anaemia was the most common side effect (731/2475, 29.5%) and represented (731/149 816, 0.5%) in all the treated patients. SOF/RBV (588/21 835, 3%) was the highest causing regimen (Figure 2). Hyperbilirubinemia was the second most common side effect (463/2475, 19%) and represented (463/149 816, 0.3%) in all the treated patients. SOF/RBV was the highest causing regimen (353/21 835, 1.6%; Figure 2). Table 2 describes the different side effects of the different drug regimen. Patients who developed side effects on SOF/RBV showed anaemia in (n = 588/1765, 33%) and hyperbilirubinemia in (353/1765, 20%) as the common side effects. One patient developed pericardial effusion and another one had an attack of myocardial infarction. One patient complained of blood sugar disturbance and three died of diabetic comas. On the same regimen, three patients developed acute renal impairment and one developed pancreatic cancer. SOF/DCV/RBV also showed hepatobiliary complications in 31% of the developed side effects, and were (92/45 188, 0.2%) in that treated patients' group. Haematological complications were (96/45 188, 0.2%) in treated patients, with anaemia being the most common one (76/45 188, 0.16%) in treated patients. Respiratory disturbances were also reported in that group of patients. Patients on SOF/SIM had anaemia in (16%) of the developed side effects, (0.2%) of the treated patients' group, while hepatobiliary complications were (40%) of the developed side effects, (0.4%) of the treated patients with hyperbilirubinemia accounted for (24%, $P = 0.058$), one patient had angiomatous oedema and two patients had photosensitivity. Patients on SOF/DCV had the lowest side effects, haematological and hepatobiliary were (0.04%) and (0.04%) of the treated patients. One patient developed leukaemia (Table 2). Only 5 patients on PVT/OBV/r/RBV regimen developed side effects, one had anaemia, one had hyperbilirubinemia and 3 patients had non-specific side effects.

### 3.4 | Management of treatment due to serious adverse events

Patients on SOF/RBV had the highest incidence of serious side effects of all regimens (n = 1227, 73%, $P < 0.001$). Secondary to serious side effects, treatment stopped in (50%, $P = 0.003$) of patients, continued in 37% and in 13% of patients, the dose of RBV decreased or stopped with increasing the duration of treatment to 24 weeks. In SOF/DCV/RBV treatment stopped in (73%, $P < 0.001$), continued in (25%) and RBV dose change (dose decrease or RBV stoppage) was in 2% of patients. Patients on SOF/SIM and SOF/DCV stopped treatment in 50% and continued in 50%. Anaemia was the most common serious side effect (n = 731/1689, 43%) with SOF/RBV the most common causing regimen (80%, $P < 0.001$). Patients with no serious side effects to DAA treatment continued treatment until W12 and W24 in comparison to those with anaemia and hyperbilirubinemia (log rank <0.001; Figure 3). Treatment discontinuation with anaemia was more common than with hyperbilirubinemia (log rank = 0.005).

### 3.5 | Adverse events were more common in cirrhotic patients

The incidence of serious side effects was higher in patients with liver cirrhosis than those without (1409/1999, 71%; log rank = 0.045; Figure 4). Similarly, the incidence of mortality was higher in patients with liver cirrhosis than those without (79/1999, 4%, log rank = 0.025).

### 3.6 | Mortality-related DAA regimens

Mortality was reported in (85/149 816, 0.06%) of the all the treated patients and (85/2475 [3.4%]) of patients with side effects. SOF/RBV

**TABLE 1** Baseline characteristics of the study cohort

| | SOF/RVB (N = 1765) | SOF/DCV (N = 150) | SOF/DCV/RBV (N = 267) | SOF/SIM (N = 288) |
|---|---|---|---|---|
| Age | 54 ± 8 | 55 ± 9 | 54 ± 9 | 55 ± 9 |
| Male, N (%) | 965 (55) | 62 (42) | 135 (51) | 156 (55) |
| BMI (kg/m$^2$) | 30 ± 5 | 31 ± 6 | 29 ± 5 | 31 ± 6 |
| Diabetes mellitus, N (%) | 375 (21) | 18 (12) | 44 (17) | 49 (17) |
| Hypertension, N (%) | 82 (5) | 16 (11) | 21 (8) | 15 (5) |
| Naïve/experienced (%) | 87/13 | 94/6 | 79/21 | 87/13 |
| History of HCC, N (%) | 2 (0.1) | — | 1 (0.4) | — |
| Hepatic encephalopathy, N (%) | 10 (0.6) | — | — | 3 (1) |
| Laboratory | | | | |
| Hemoglobin (g/dL) | 13 ± 1.6 | 13 ± 1.6 | 13 ± 1.7 | 13 ± 1.8 |
| TLC $\times 10^3/\mu L$ | 4.8 ± 1.8 | 6 ± 2 | 5.3 ± 2.2 | 5.6 ± 2.1 |
| ANC $\times 10^3/\mu L$ | 7.8 ± 1.2 | 3.3 ± 1.6 | 2.9 ± 1.5 | 2.9 ± 1.4 |
| Platelets $\times 10^3/\mu L$ | 106 ± 52 | 216 ± 67 | 132 ± 60 | 138 ± 65 |
| INR | 1.3 ± 0.2 | 1.1 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.2 |
| AST (IU/L) | 81 ± 52 | 48 ± 36 | 70 ± 42 | 71 ± 45 |
| ALT (IU/L) | 63 ± 42 | 49 ± 33 | 58 ± 34 | 57 ± 39 |
| Bilirubin (mg/dL) | 1.3 ± 0.8 | 0.8 ± 0.3 | 1.1 ± 0.5 | 1.1 ± 0.5 |
| Albumin (g/dL) | 3.5 ± 0.6 | 4.1 ± 0.5 | 3.7 ± 0.5 | 3.7 ± 0.6 |
| Creatinine (mg/dL) | 0.9 ± 0.3 | 0.8 ± 0.2 | 0.9 ± 0.6 | 0.9 ± 0.4 |
| HCV RNA log10 IU/mL | 5.38 ± 0.87 | 5.60 ± 0.85 | 5.51 ± 0.92 | 5.6 ± 0.9 |
| Child-Pugh score | | | | |
| A/B/C (%) | 77/22/0.3 | 97/3/0 | 88/12/0 | 93/7/0 |
| US features | | | | |
| Liver cirrhosis, N (%) | 1576 (89) | 39 (26) | 182 (68) | 201 (70) |
| Splenomegaly, N (%) | 1243 (71) | 0 | 0 | 132 (46) |
| Ascites, N (%) | 11 (0.6) | 1 (0.7) | 4 (1.5) | 1 (0.3) |
| Liver fibrosis stage | | | | |
| LSM-TE (kPa), N = 344 | 25.4 ± 15.7 | 13 ± 10.5 | 19.5 ± 11.9 | 21.4 ± 15.1 |
| FIB-4, N = 2458 | 6.64 ± 7.73 | 2.11 ± 3.22 | 4.97 ± 4.3 | 5.01 ± 4.06 |
| Upper endoscopy | | | | |
| Free/varices/PHG/not performed | 14/40/2/44 | 2/1/0/97 | 3/3/0/94 | 7/14/0.3/79 |

The baseline characteristics of the study cohort according the different treatment regimens. Data are given as *M* ± SD. Patients on SOF/RBV regimen had the highest cirrhosis rate, lower platelets and albumin and higher bilirubin at baseline.

DAA, direct antiviral drugs; SOF/RBV, sofosbuvir/ribavirin; SOF/DCV, sofosbuvir/daclatasvir; SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin; BMI, body mass index; TLC, total leucocytic count; ANC, absolute neutrophilic count; INR, international normalization ratio; AST, aspartate transaminase; ALT, alanine transaminase; US, ultrasonographic; LSM, liver stiffness measurement; TE, transient elastography, PHG, portal hypertensive gastropathy.

regimen had the highest death rate (54/85 [64%], $P = 0.713$), and (54/21 835 [0.3%]) in that treated patients' group, followed by SOF/SIM (24/85 [28%]) and SOF/DCV/RBV (7/85 [8.2%]), while SOF/DCV and PTV/OBV/r/RBV showed no mortality. Patients who were on SOF/RBV and died, had pre-treatment thrombocytopenia in 54%, 15% oesophageal varices and one patient was cardiac, two patients had pre-treatment anaemia (4%). Patients on SOF/SIM regimen had 33% pretreatment thrombocytopenia, 38% pre-treatment varices. Patients who received SOF/DCV/RBV had 17% pre-treatment thrombocytopenia. DAA treatment discontinuation was highest at week 4 (37%, $P < 0.001$).

### 3.7 | Factors predicting serious adverse effects

To predict factors associated with development of serious side effects during DAA treatment, demographic, laboratory, and clinical factors before treatment were evaluated; multivariate analysis revealed that male gender, lower haemoglobin, platelets and albumin,

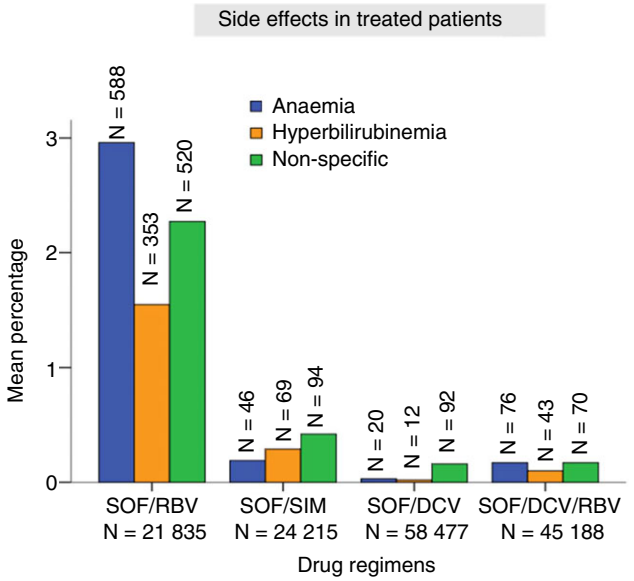



**FIGURE 2** Comparison of anaemia, hyperbilirubinemia and other nonspecific side effects in each drug regimen as regard to total number of treated patients. Percentage of anaemia and hyperbilirubinemia was highest in the SOF/RBV regimen, while the SOF/DCV regimen showed the least percentage of the side effects. SOF/RBV, sofosbuvir/ribavirin; SOF/DCV, sofosbuvir/daclatasvir; SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin; SOF/SIM, sofosbuvir/simeprevir; N, number

higher bilirubin, higher Child-Pugh score, presence of liver cirrhosis before treatment were factors associated with serious side effects development during DAA treatment (Table 3). Regarding the regimens, lower platelets and the presence of liver cirrhosis were factors predicting serious side effects in SOF/DCV, while the presence of cirrhosis was the only factor associated with serious side effects in the SOF/DCV/RBV regimen. Lower platelet count, higher bilirubin and the presence of liver cirrhosis were the factors associated with serious side effects in the SOF/RBV regimen, while only lower platelet count was the only factor associated with side effects development in the SOF/SIM regimen (Table 4).

### 3.8 | Non-significant incidence of HCC development under DAA treatment

Hepatocellular cellular carcinoma developed in 33/149 816 patients (0.02%) who were treated with DAA regimens which represented 33/2475 of patients with side effects (1.3%). 25/33 patients (76%, $P = 0.243$) were treated with the SOF/RBV regimen and represented 25/21 835 patients (0.1%) of the treated SOF/RBV patients.

## 4 | DISCUSSION

To our knowledge, this is the first study with such a large cohort of chronic HCV-infected patients treated with DAAs who reported associated adverse effects and related death. This study revealed that interferon-free regimens are associated with minimal side effects, which are mostly non-serious. The most common side effects were haematological complications, with anaemia being the dominant one, particularly with respect to the SOF/RBV regimen. The serious haematological adverse effects were managed with haematopoietic agents, treatment discontinuation or reduction in RBV dose with prolongation of treatment duration. The SOF/RBV regimen showed the highest rate of side effects, with anaemia being the prominent one. The SOF/SIM regimen was associated with hyperbilirubinemia; however, this was not significant and did not require treatment discontinuation or a change in drug dosage. DCV-containing regimens showed the lowest side effects among all regimens. This study also showed that death was highest in the SOF/RBV regimen and pre-treatment thrombocytopenia and higher Child score were the dominant pre-treatment associated pathologies. In this study, HCC was reported in 33 patients, and this was mostly with the SOF/RBV regimen; however, this was not significant. Serious adverse effects as well as death were prominent with liver cirrhosis under the interferon-free regimens irrespective of the regimen.

The initial approval of DAAs by the Egyptian Council Committee of Viral Hepatitis had dramatically improved the SVR rate in Egyptian chronic HCV-infected patients, from 60% to almost 100% in some studies.[5,8,10] Our study showed that SVR24 reached 88% in those who developed side effects. Although the majority of the study cohort were cirrhotic patients (81%), side effects development was minimal (1.7%), in comparison to other studies, the entire cohort of which were cirrhotic patients and reported 24% side effects.[16] Serious side effects that led to reduction in the RBV dose and prolongation of the treatment duration or even treatment discontinuation, were observed in only (1.1%) of cases. Anaemia was the most common serious side effect, and was mostly associated with the SOF/RBV regimen. The rate of serious side effects was lower in comparison to that of the Guard-C study, which reported 5.9% serious side effects, while the incidence of anaemia in our study was higher (29.5% vs 25%).[17] Interestingly, our multivariate analysis confirmed that pre-treatment HB (<12.6 g/dL) and lower platelets ($124 \times 10^3$/μL) were associated with post-treatment serious side effects development, as previously mentioned.[18] Our large cohort also revealed that the pre-treatment higher Child-Pugh score represented in lower albumin <35 g/dL and higher bilirubin >1.2 μmol/dL were also factors associated with post-treatment serious side effects development. Lower albumin was also described by Maan et al and Foster et al as factors associated with post-treatment serious side effects development.[16,17]

The second common serious side effect was hyperbilirubinemia, which was not significant and was only prominent in the SOF/RBV regimen. Non-specific side effects such as fatigue, headache and abdominal discomfort were the most commonly reported in all regimens, which is line with all previously published data.[5,7,8,10,16,19,20]

Death was reported in only 0.06% of all treated patients, and was mainly associated with the SOF/RBV regimen. Death was in most of the cases secondary to hepatic decompensation. Three

**TABLE 2** Adverse effects of DAA according to the drug regimen in the study cohort

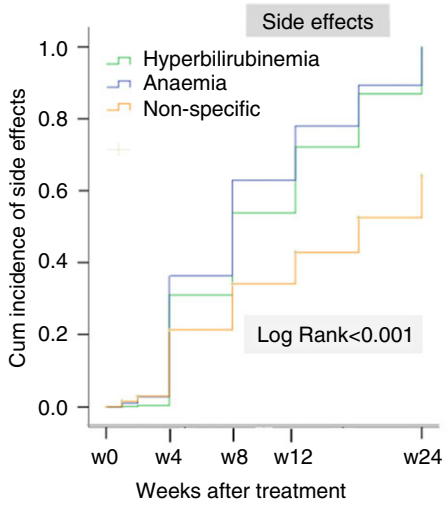
| | SOF/RVB (N = 21 835) | SOF/RVB (N = 1765) | SOF/DCV (N = 58 477) | SOF/DCV (N = 150) | SOF/DCV/RBV (N = 45 188) | SOF/DCV/RBV (N = 267) | SOF/SIM (N = 24 215) | SOF/SIM (N = 288) |
|---|---|---|---|---|---|---|---|---|
| Hematological | 616 (2.8) | | 22 (0.04) | | 96 (0.2) | | 48 (0.2) | |
| Anaemia | 588 (2.7) | 588 (33.2) | 20 (0.03) | 20 (13.3) | 76 (0.16) | 76 (28.5) | 46 (0.2) | 46 (16) |
| Neutropenia | 4 (0.02) | 4 (0.2) | — | — | 1 (0.00) | 1(0.4) | 1 (0.00) | 1 (0.4) |
| Thrombocytopenia | 24 (0.1) | 24 (1.4) | 2 (0.00) | 2(1.4) | 19 (0.04) | 19 (7.1) | 2 (0.01) | 2 (0.7) |
| Metabolic | 4 (0.02) | | — | | — | | — | |
| Blood sugar disturbance | 1 (0.01) | 1 (0.1) | — | — | — | — | — | — |
| Diabetic coma | 3 (0.01) | 3 (0.2) | — | — | — | — | — | — |
| Gastrointestinal | | | — | | — | | | |
| Abdominal discomfort | 4 (0.02) | 4 (0.2) | — | — | — | — | 3 (0.01) | 3 (1.0) |
| Dry mouth | — | — | — | — | 2 (0.00) | 2 (0.7) | — | — |
| Respiratory | | | — | — | 4 (0.01) | | — | |
| Dyspnea | | | — | — | 2 (0.00) | 2 (0.7) | — | — |
| Pleural effusion | 1 (0.01) | 1 (0.1) | — | — | | | — | — |
| Pneumonia | — | — | — | — | 1 (0.00) | 1 (0.4) | — | — |
| Dry cough | — | — | — | — | 1 (0.00) | 1 (0.4) | — | — |
| Cardiovascular | 2 (0.02) | | — | — | — | | — | |
| Pericardial effusion | 1 (0.01) | 1 (0.1) | — | — | — | — | — | — |
| Myocardial infarction | 1 (0.01) | 1 (0.1) | — | — | — | — | — | — |
| Non-specific | 10 (0.04) | | 6 (0.01) | | 5 (0.01) | | 15 (0.06) | |
| Headache | 4 (0.02) | 4 (0.2) | 1 (0.00) | 1 (0.7) | 2 (0.00) | 2 (0.7) | 6 (0.03) | 6 (2.2) |
| Fatigue and weakness | 3 (0.01) | 3 (0.2) | 2 (0.00) | 2 (1.3) | 2 (0.00) | 2 (0.7) | 4 (0.02) | 4 (1.4) |
| Photosensitivity | — | — | 4 (0.00) | 4 (2.7) | — | — | 2 (0.01) | 2 (0.7) |
| Pruritus | 3 (0.01) | 3 (0.2) | 1 (0.00) | 1 (0.7) | 1 (0.00) | 1 (0.4) | 4 (0.02) | 4 (1.5) |
| Angiomatous edema | — | — | — | — | — | — | 1 (0.01) | 1 (0.4) |
| Acute renal impairment | 3 (0.01) | 3 (0.2) | 1 (0.00) | 1 (0.7) | — | — | 1 (0.00) | 1 (0.4) |
| Hepatobiliary | 550 (4.62) | | 26 (0.04) | | 92 (0.2) | | 99 (0.40) | |
| Liver enzymes | 32 (0.1) | 32 (1.8) | 8 (0.01) | 8 (5.3) | 19 (0.04) | 19 (7.1) | 9 (0.04) | 9 (3.1) |
| Hepatic causes | 21 (0.1) | 21 (1.2) | — | — | 2 (0.00) | 2 (0.8) | 2 (0.01) | 2 (0.7) |
| PVT | 2 (0.01) | 2 (0.1) | — | — | 1 (0.00) | 1 (0.4) | 1 (0.00) | 1(0.4) |
| Ascites | 99 (0.5) | 99 (5.6) | 1 (0.00) | 1 (0.7) | 3 (0.01) | 3 (1.1) | 9 (0.04) | 9 (3.1) |
| Hepatic encephalopathy | 20 (0.1) | 20 (1.2) | — | — | 2 (0.00) | 2 (0.7) | 1 (0.00) | 1 (0.4) |
| HCC | 25 (0.1) | 25 (1.4) | 2 (0.00) | 2 (1.3) | 1 (0.00) | 1 (0.4) | 5 (0.02) | 5 (1.8) |
| Hypoalbuminemia | 9 (0.04) | 9 (0.5) | 3 (0.00) | 3 (2.0) | 12 (0.03) | 12 (4.5) | 3 (0.01) | 3 (1.1) |
| Hyperbilirubinemia | 353 (1.6) | 353 (20) | 12 (0.02) | 12 (8.0) | 43 (0.10) | 43 (16.1) | 69 (0.28) | 69 (24) |
| Bleeding | 4 (0.02) | 4 (0.2) | — | — | — | — | 1 (0.00) | 1 (0.4) |
| Malignancy | 1 (0.01)[a] | 1 (0.1)[a] | 1 (0.00) | 1 (0.7)[b] | — | — | | — |
| Death | 54 (0.3) | 54 (3.1) | — | — | 7 (0.2) | 7 (2.6) | 24 (0.10) | 24 (8.3) |
| Others | 520 (2.4) | 520 (30.1) | 92 (0.16) | 92 (61.3) | 70 (0.15) | 70 (26.2) | 94 (0.39) | 94 (33.0) |

The hematological, hepatic causes and non-specific side effects among the different DAA regimens, anemia was highest in SOF/RBV while hepatobiliary complications were most common in SOF/SIM regimen. Cardiovascular and blood sugar disturbance as well as diabetic coma were reported only with SOF/RBV, while photosensitivity cases were reported in SOF/DCV and SOF/SIM regimens.

DAA, direct antiviral drugs; SOF/RBV, sofosbuvir/ribavirin; SOF/DCV, sofosbuvir/daclatasvir; SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin; SOF/SIM, sofosbuvir/simeprevir; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis.

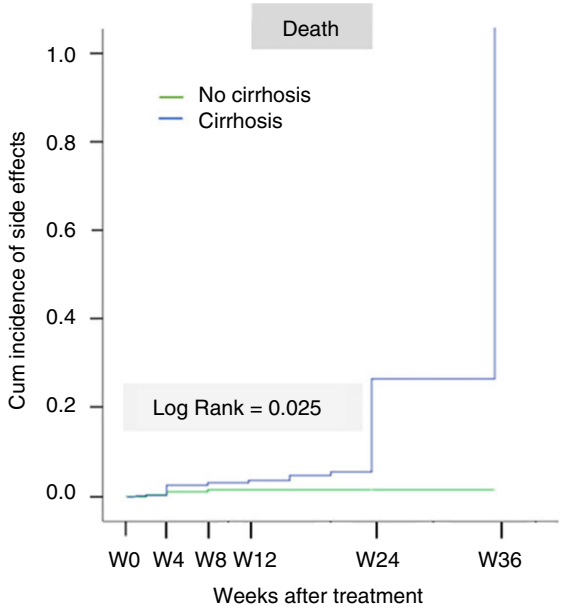
[a]A case of pancreatic cancer was reported with SOF/RBV regimen.

[b]A case of leukemia was reported in SOF/DCV. Respiratory complications were reported in patients with SOF/DCV/RBV regimen.




| Adverse effects | W4 | W8 | W12 | W24 |
|---|---|---|---|---|
| Hyperbilirubinemia | 168 | 122 | 69 | 111 |
| Anaemia | 223 | 165 | 132 | 201 |
| Non-specific | 648 | 309 | 135 | 159 |

**FIGURE 3** Comparison of timing of treatment discontinuation between anaemia, hyperbilirubinemia and nonspecific side effects. Percentage of patients with nonspecific side effects who stopped treatment was significantly lower in comparison to those with anaemia and hyperbilirubinemia throughout the follow-up period (log rank <0.001). W, week.




| | W4 | W8 | W12 | W24 | W36 |
|---|---|---|---|---|---|
| Cirrhosis | 51 | 7 | 4 | 16 | 1 |
| No cirrhosis | 5 | 1 | 0 | 0 | 0 |

**FIGURE 4** Comparison between patients with and without cirrhosis as regard the incidence of death. The percentage of patients with liver cirrhosis had a higher incidence of death than those without liver cirrhosis (log rank = 0.025). W, week.

patients died due to diabetic coma and one due to myocardial infarction under the SOF/RBV regimen.

Hepatocellular carcinoma was also reported in 0.02% of all treated patients, and most cases were reported in the SOF/RBV regimen. This incidence is, however, lower when compared to other studies.[21,22] The incidence of HCC on this regimen can be explained by the associated liver cirrhosis in 89% of patients, which is line with previous published data,[23] and 22% were Child-Pugh B, which may favour disease progression and the presence of regenerative nodules before the start of treatment. It is to be noted, that the presence of cirrhosis was associated with increased death rate and was also the common factor detected in all regimens associated with serious side effects development.

The incidence of serious side effects, death and HCC development was highest in the SOF/RBV regimen. This can be explained by the fact that this regimen was the first approved regimen for DAAs, and all patients treated with this regimen were the most sick (lower platelets and higher Child-Pugh score B). On the other hand, SOF/DCV showed the lowest incidence of side effects in comparison to the other regimens.

This study was conducted on a large cohort of Egyptian patients, more than 90% of which are infected with genotype 4.[7] Egypt is one of the countries with the highest prevalence with HCV infection, and the urgency to treat chronic HCV patients is associated with reduction in prevalence, which already started to appear, with 29% reduction in prevalence in 2015.[4] This study has several limitations; although we are reporting the adverse effects of several regimens, many of these regimens may no longer be used in several countries (eg SOF/RBV combination is no longer recommended in the European and American guidelines). Moreover, SIM is also rarely in use today, not due to efficacy but because of economic reasons. We must highlight that SIM is still used in many regions including Egypt. Another point to highlight is that these data were excluded from the database which were reported by the treating physicians. There may be an underreporting of adverse effects because there was no soft data verification by independent physicians; however, this is also accepted in large cohort studies. In conclusion, the use of PEG-IFN/RBV combination was limited due to eligibility, tolerability and treatment efficacy (40%-69%).[24,25] The use of interferon-free regimens increased the SVR rate and improved the tolerability and eligibility of treatment. The use of interferon-free regimens is safe and tolerable, with a higher cure rate in patients with genotype 4 than the previously used regimen. Cirrhotic patients are in particularly urgent need of treatment and those regimens are the most safely used, but this requires close monitoring and the use of haematopoietic agents to avoid anaemia, especially with RBV-containing regimens. Regular sonographic assessment for early detection of HCC is also of great importance in patients with liver cirrhosis. Future worldwide studies are required to address the adverse effects caused by the new regimens used today, such as SOF/velpatasvir, grazoprevir/elbasvir and glecaprevir/pibrentasvir.

**TABLE 3** Uni and multivariate analysis predicting factors associated with serious side effects development

| | | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|
| | **Side effects** | **Values** | ***P*-value** | **Odds ratio** | ***P*-value** | **Odds ratio** |
| Male gender | Serious SE | 63% | 0.001 | 1.334 | 0.012 | 1.277 |
| | No serious SE | 37% | | | | |
| Haemoglobin | Serious SE | 12.7 ± 1.61 | <0.001 | 0.821 | <0.001 | 0.888 |
| | No serious SE | 13.2 ± 1.64 | | | | |
| Platelets | Serious SE | 124 ± 60 | <0.001 | 0.994 | <0.001 | 0.996 |
| | No serious SE | 164 ± 72 | | | | |
| Bilirubin | Serious SE | 1.2 ± 0.5 | 0.001 | 1.336 | 0.002 | 1.297 |
| | No serious SE | 0.9 ± 0.6 | | | | |
| Albumin | Serious SE | 3.5 ± 0.5 | <0.001 | 0.596 | 0.001 | 0.690 |
| | No serious SE | 3.9 ± 0.5 | | | | |
| Child-Pugh score | Serious SE | 4.7 ± 2.5 | <0.001 | 1.159 | 0.001 | 0.727 |
| | No serious SE | 3 ± 3 | | | | |
| Cirrhosis | Serious SE | 70% | <0.001 | 2.544 | <0.001 | 8.668 |
| | No serious SE | 30% | | | | |

This table revealed that in the multivariate analysis male gender, lower haemoglobin and platelets and albumin, higher bilirubin and Child-Pugh score, the presence of cirrhosis were factors associated with serious side effects development during any DAA regimen treatment. SE, side effects.

**TABLE 4** Multivariate analysis of serious side effects development according to the drug regimens

| | **SOF/DCV**<br>***P*-value**<br>**Odds ratio (95% CI)** | **SOF/DCV/RBV**<br>***P*-value**<br>**Odds ratio (95% CI)** | **SOF/RBV**<br>***P*-value**<br>**Odds ratio (95% CI)** | **SOF/SIM**<br>***P*-value**<br>**Odds ratio (95% CI)** |
|---|---|---|---|---|
| Male gender | 0.09<br>1.92 (0.25-1.11) | 0.94<br>1.01 (0.70-1.39) | 0.65<br>0.94 (0.82-1.37) | 0.87<br>0.97 (0.73-1.45) |
| Heamoglobin | 0.72<br>1.04 (0.84-1.29) | 0.94<br>1.00 (0.90-1.12) | 0.77<br>0.99 (0.91-1.07) | 0.93<br>1.01 (0.90-1.12) |
| Platelets | **<0.001**<br>**1.01 (1.01-1.02)** | 0.76<br>1.00 (0.99-1.00) | **<0.001**<br>**0.99 (0.99-1.00)** | **0.03**<br>**1.00 (1.00-1.01)** |
| INR | 0.11<br>0.24 (0.11-1.59) | 0.23<br>0.60 (0.26-1.39) | 0.78<br>1.09 (0.60-1.99) | 0.19<br>1.66 (0.77-3.58) |
| Bilirubin | 0.12<br>0.51 (0.22-1.19) | 0.22<br>0.84 (0.63-1.11) | **0.02**<br>**1.28 (1.04-1.58)** | 0.16<br>0.82 (0.62-1.09) |
| Albumin | 0.217<br>1.62 (0.75-3.47) | 0.49<br>0.89 (0.64-1.24) | 0.59<br>1.07 (0.84-1.37) | 0.92<br>0.98 (0.71-1.36) |
| Cirrhosis | **<0.001**<br>**0.42 (2.01-8.84)** | **<0.001**<br>**2.27 (1.48-3.48)** | **<0.001**<br>**0.36 (0.26-0.51)** | 0.42<br>1.02 (0.76-1.96) |

This table revealed that in the multivariate analysis; lower platelets, the presence of cirrhosis was associated factors with SE in the SOF/RBV regimen, while in SOF/DCV/RBV; the presence of cirrhosis was the associated factor predicting serious side effects. In SOF/RBV; lower platelets, higher bilirubin and the presence of cirrhosis were the factors associated with serious side effects development. In SOF/SIM regimen; lower platelet count was the only factor associated with serious side effects.
SOF/DCV, sofosbuvir/daclatasvir; SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin; SOF/RBV, sofosbuvir/ribavirin; SOF/SIM, sofosbuvir/simeprevir; INR, international normalisation ratio; OR, odds ratio.

## ACKNOWLEDGEMENT

*Declaration of personal and funding interests:* None.

## AUTHORSHIP

*Guarantor of the article:* Gamal Esmat.

*Author contributions:* Dina Attia, Heiner Wedemeyer and Gamal Esmat designed the concept of the study. Dina Attia and Heiner Wedemeyer wrote the manuscript, analysed and interpreted the data. All other authors collected the data. All authors reviewed the manuscript and approved the final version to be published.

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**How to cite this article:** Attia D, El Saeed K, Elakel W, et al. The adverse effects of interferon-free regimens in 149 816 chronic hepatitis C treated Egyptian patients. *Aliment Pharmacol Ther*. 2018;00:1–10. https://doi.org/10.1111/apt.14538