

## Safety and Efficacy of Direct Acting Antivirals (Sofosbuvir & Daclatasvir) in treatment of Chronic HCV in HIV-HCV Co-Infected Egyptian Patients

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### ABSTRACT

**Background:** Liver-related mortality is considered the most common cause of death in HIV/HCV-co infected individuals. Accordingly, treatment of HCV infection in HIV/HCV-co infected individuals is a priority to manage such major health burden.

**Objectives:** To evaluate the safety and efficacy of treatment of chronic HCV by DDAs in HCV-HIV co-infected Egyptian patients.

**Patients and methods:** It is an observational study that included 22 patients; only 18 HCV\HIV co-infected patients completed the study [14 males (77.8 %) and 4 females (22.8 %)]. Their ages ranged from 21 to 46 years with a mean age of 32.89 years. Half of them married and 72% of them working. 61% of them are smokers and IV addicts. Patients were divided into two groups according to HIV PCR. Group I included 12 Patients with HIV PCR > 50 copies/mm and group II that included 6 patients with HIV PCR < 50 copies \mm.

**Results:** The rates of a sustained virologic response (SVR) at post-treatment week 12 (SVR 12) were high [17/18 (94.4%)]. The most common adverse events were fatigue (66.7%), headache (50%) and there was a high safety profile on using direct-acting antivirals (DAAs) and no patient discontinued treatment because of adverse events. No serious adverse events or mortality was reported. In addition, AST & ALT were significantly decreased at end of treatment and 12 weeks after treatment. Otherwise there were no significant changes in both hematological and chemistry labs.

**Conclusions:** Daclatasvir plus sofosbuvir for 12 weeks resulted in a high rate of sustained virologic response in patients co infected with HIV and HCV with high safety profile after treatment completion.

**Keywords:** Daclatasvir, sofosbuvir, sustained virologic response, HCV/HIV co infection.

### INTRODUCTION

According to United Nations Program on HIV/AIDS (UNAIDS), there were 8,800 people living with HIV/AIDS in Egypt by the end of 2014 <sup>(1)</sup>.

With the wide spread of antiretroviral therapy, the effect of HIV co-infection on the course of HCV disease is reduced but not eliminated by antiretroviral therapy. On the other hand, liver-related mortality is considered the most common cause of death in HIV/HCV-co infected individuals. Accordingly, treatment of HCV infection in HIV/HCV-co infected individuals is a priority to manage such major health burden <sup>(2)</sup>.

Hepatitis C virus treatment can eradicate infection achieving sustained virological response (SVR), defined as undetectable HCV ribonucleic acid (RNA) in the blood 12 weeks after the completion of HCV treatment. This is strongly associated with reduced risk of liver-related morbidity and mortality such as hepatocellular carcinoma (HCC) or liver transplantation <sup>(3)</sup>.

Among HIV/HCV-coinfected patients, HCV treatment in the era of interferon-based regimens was marked by poor tolerability, frequent serious adverse events like, bone marrow depression and flu-like symptoms (e.g., fever, chills, headaches, arthralgia, and myalgia). In addition, neuropsychiatric disorders (e.g., severe fatigue, irritability and apathy), neurological side effects (e.g., seizures, paresthesia, confusion,

aphasia, cortical blindness, delirium and extrapyramidal syndromes marked by ataxia), autoimmune syndromes, complex drug interactions, and limited efficacy with SVR rates of 20%–29% in patients with HCV genotype 1 infection <sup>(4)</sup> are recorded.

The development of pegIFN-free oral regimens of direct-acting antivirals (DAAs) greatly improved the efficacy and tolerability of HCV treatment in co-infection. The combination of daclatasvir (DCV) + sofosbuvir (SOF) without ribavirin (RBV) for 12 weeks showed a high rate of sustained virological response (SVR) with good tolerability in HIV–HCV-co-infected patients treated with a wide range of cART <sup>(5)</sup>.

The aim of this study is to evaluate the safety and efficacy of treatment of chronic HCV by DAAs in HCV-HIV co-infected Egyptian patients.

### PATIENTS AND METHODS

- **Type of the study:** Observational study.
- **Study period:** 6 months.
- **Site of the study:** Abbasia Fever Hospital.
- **Sample size:** 18 cases
- **Inclusion criteria:** Age > 18 years. HCV RNA positive. HIV infection confirmed by western blot.
- **Exclusion Criteria:** Child C cirrhotic patients, platelet count < 50000/mm<sup>3</sup>, patients with HCC, pregnancy and uncontrolled diabetes mellitus (HbA1c > 9%).



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- **Process:**
- Eligible patients received treatment regimens assigned by National Committee for Control of Viral Hepatitis (NCCVH). They are categorized into:

**1-Easy to treat group:**

- Treatment naïve.
- Total serum bilirubin < 1.2 mg / dl
- INR < 1.2
- Platelet count > 150000/ mm

**2-Difficult to treat group:**

- Peg-INF treatment experienced
- Total serum bilirubin > 1.2 mg / dl
- INR > 1.2
- Platelet count < 150000/ mm

**Treatment regimens that were received:**

(For HCV according to NCCVH )

- Easy to treat: Sofosbuvir/ Daclatasvir.
- Difficult to treat: Sofosbuvir/ Daclatasvir/ ribavirin.

**Tools:**

All included patients are subjected to the following before starting the treatment:

- Full history taking.
- Complete clinical examination.
- Pelvi-abdominal U/S to assess liver.
- Laboratory investigations including: AST, ALT, Total Bilirubin, Serum albumin, INR, Serum creatinine, CBC, Alfa feto protein & HCV RNA by PCR.
- Evaluation of HIV condition before treatment by:
  - HIV RNA by PCR.

**Steps of performance:**

- Complete history taking.
- Full clinical examination.
- Analysis of the results.
- Laboratory data before treatment to be compared with those done during & after treatment.
- Preparing conclusions and recommendations.

**Ethical and patients' approval:**

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

**Statistical Analysis**

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version **25.0**. Qualitative data were represented as frequencies and relative percentages. Continuous data were presented as Mean ± SD if normally distributed or Median (Range) if not normally distributed. Categorical data were presented by the frequency and percentage.

Normality was checked by Kolmogorov-Smirnov test. Homogeneity of variances was checked by Leven's test. Kruskal-Wallis H test and ANOVA (F test) for normal quantitative variables, to compare between more than two groups. Post Hoc test (LSD) for pairwise comparisons. Threshold for significance *P*-value ≤ .05 indicates significant, *P* ≤ .01 indicates highly significant difference. *P* > .05 indicates non-significant difference.

**RESULT**

**Table (1):** Distribution of the studied patients according to their antiviral medication for hepatitis C , HIV infection and HIV PCR

	N (18)	%
<b>DAA for HCV:</b>		
• Dual	15	83.3
• Triple	3	16.7
<b>Anti HIV agents:</b>		
• Truvada + Efavirenz	16	88.9
• Lamivudine + Efavirenz	2	11.1
<b>HIV PCR:</b>		
• < 50	12	66.7
• > 50	6	33.3

Table (1) showed that about 83% of the studied patients were eligible to dual therapy protocol of sovosbuvir and daclatasvir. About 89% of them used Truvada & Efavirenz as anti HIV medications, regarding HIV PCR, two thirds of the studied patients had its level < 50.

**Table (2):** Distribution of the studied patients according to HCV PCR before, by the end of treatment and after 12 weeks

	Mean ± SD	Median (Range)
<b>PCR before ttt</b>	2521212.89 ± 3569521.7	1195500 (1320 – 14947033)
	<b>N (18)</b>	<b>%</b>
<b>By the end of treatment:</b>		
• Negative	18	100
• Positive	0	0
<b>SVR at 12 weeks:</b>		
• Negative	17	94.4
• Positive (relapse)	1	5.6

Three months after starting treatment, all the studied patients had negative HCV PCR, yet 3 months after ending of treatment only one case had relapse. The patient with relapse had an inherited bleeding disorder (hemophilia), which is considered an important risk factor due to contaminated blood products. Another possible explanation of the relapsed case is the high viral load of HCV (more than 14 million IU per milliliter) as shown in table (2).

**Table (3):** Distribution of the studied patients according to adverse effects:

	N (18)	%
<b>Adverse effect:</b>		
• Headache	9	50
• Fatigue	12	66.7
• Nausea	5	27.8
• Diarrhea	5	27.8
• Pruritus	3	16.7
• insomnia	5	27.8

Table (3) showed that the most common adverse effects occurred in the studied patients were fatigue (66.7%), followed by headache (50%) then nausea, diarrhea and insomnia (27.8% each).

**Table (4):** Change in liver and kidney function tests findings over time among the studied patients

	Before		By the end of treatment		After 12 weeks		F	p
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median		
<b>ALT (U/L)</b>	53.22±4.79 <sup>∞</sup>	41	34.44 ± 3.34	33	31.56±2.11 <sup>∞</sup>	31.2	Fr 16.3	<0.001**
<b>AST (U/L)</b>	44.06 ± 2.35	39.5 <sup>∞</sup>	35.39 ± 1.88	37	34.44 ± 1.4	36.5	Fr16.44	<0.001**
<b>Serum albumin (mg/dl)</b>	4.31 ± 0.39		4.19±0.29		4.23 ± 0.26		2.494	0.114
<b>Total bilirubin (mg/dl)</b>	0.8 ± 0.18		0.76 ± 0.13		0.69 ± 0.14		3.214	0.067

F repeated measure ANOVA Fr Friedman test \*p<0.05 is statistically significant  
\*\*p<0.001 is statistically highly significant

There was significant decrease in ALT and AST over time in the studied patients. On pairwise comparison, there was significant change between ALT levels before and 12 weeks after treatment. On the other hand, there was non-significant change in serum albumin and total bilirubin over time.

## DISCUSSION

The current study included eighteen patients, their ages ranged from 21 to 46 years old with mean age 32.89 years. More than 77% of them were males. Half of them were married and 72.2% were working. More than 60% of them were smokers and addicted to IV substances. All of them were HIV–HCV coinfecting patients and received 12 weeks of daclatasvir plus sofosbuvir, 94.4% of them had a sustained virologic response at week 12 post-treatment (SVR 12).

The rate of sustained virologic response is noted to be higher than the results of real-life cohort study conducted by **Milazzo and his colleges** <sup>(6)</sup>. They found that the SVR 12 in HIV/HCV co-infected patients who received oral DAAs regimens (25% received sofosbuvir and daclatasvir combination) were about 91%.

On the other hand, SVR rate reported in the current study is lower than the high rates observed by **Wyles et al.** <sup>(7)</sup> study.

**Panel et al.**, <sup>(8)</sup> also found that both Daclatasvir and sofosbuvir have limited pharmacokinetic interactions with other antiretroviral drugs. There were no drug interactions with tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, stavudine, rilpivirine, raltegravir, dolutegravir or maraviroc.

In the current study, the majority 88.9% of the enrolled patients (16 patients) received antiretroviral combination of truvada and efavirenz, (2 patients) were receiving antiretroviral combination of lamivudine and efavirenz. In addition, there were no drug interactions between DAAs and ARVs.

In the era of IFN-based regimens, SVR was related to several patient and treatment characteristics including body mass index (BMI), stage of fibrosis, baseline viral load, early virologic response, previous failure of IFN-based therapy, treatment duration and use of ribavirin <sup>(9)</sup>. While, in the era of DAAs based therapy, baseline viral load, previous interferon experience, and the use of RBV were reported to exert not effect on, treatment efficacy <sup>(10)</sup>.

In our study, all the three patients who received RBV with sofosbuvir and daclatasvir had HCV RNA undetected at 12 weeks.

Our results also agree with **Wyles et al.** <sup>(7)</sup> in reporting higher relapse rate among patients who had a high baseline HCV RNA level.

**Elsharkawy et al.** <sup>(11)</sup> and **Bachofner et al.** <sup>(12)</sup> reported that there was a significant decline in the necroinflammation markers (AST and ALT) 12 weeks after ending of treatment by sofosbuvir based regimens. Improvement of AST and ALT may be explained by temporary reduction in viral replication, which is sufficient to decrease the necroinflammation markers <sup>(13)</sup>. This agrees with our study that showed a significant decrease in ALT and AST over time in the studied patients 12 weeks after the end of treatment.

## CONCLUSION

Daclatasvir plus sofosbuvir for 12 weeks resulted in a high rate of sustained virologic response in patients co-infected with HIV and HCV with high safety profile after treatment completion with no discontinuations due to adverse effects.

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