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Challenges in treatment of Chronic HCV in HIV-HCV Co-Infected Egyptian Patients by direct acting antivirals (sofosbuvir and daclatasvir)

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ABSTRACT

Background: the most common cause of death in HIV/HCV-co infected patients' liver-related mortality. So, treatment of HCV infection in co infected individuals is considered a priority.
Objectives: to evaluate the safety and efficacy of DAAs (sofosbuvir & daclatasvir) in treating chronic HCV in HCV-HIV co-infected Egyptian patients.
Patients and methods: The study includes 18 HCV\HIV co-infected patients (14 males 77.8 % and 4 females 22.8 %). Their standard age +/- 32.89 years, 61% of them are smokers and IV addicts. Patients divided according to HIV PCR into 2 groups; Group I including 12 Patients with HIV PCR > 50 copies\mm and Group II including 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%). There was a high safety profile on using sofosbuvir & daclatasvir and no patient discontinued treatment because of adverse events. Also, AST & ALT were significantly decreased at end of treatment and 12 weeks after treatment, CD4 count was significantly increased. Otherwise there are 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: DAAs, sofosbuvir, daclatasvir, HCV, HIV, SVR.

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INTRODUCTION

HCV infection is highly prevalent among HIV-1-infected individuals. Globally, an estimated 130–170 million people are infected with the hepatitis C virus (HCV), and the virus is found in 10–30% of all people living with an HIV infection **(Wyles et al., 2016).**

According to **the Joint United Nations Programme on HIV/AIDS (UNAIDS) fact sheet, 2017**, globally about 36.7 million people are living with HIV and approximately 5 million people are co-infected with HIV and HCV **(Operskalski et al., 2011)**.

Data about the prevalence of HCV in HIV patients in Egypt are lacking, however the prevalence of HIV among HCV infected Egyptian patients was (0.66%) **(Fouad et al., 2013).** the prevalence of HCV in HIV patients is expected to be high due to extremely high background of hepatitis C prevalence in the general population as about 10% according to the most recent **Egyptian Health Issues Survey (EHIS)** in 2015 taking in consideration that according to **(Khattab et al., 2011)** genotype 4 infection accounts for more than 90% of the HCV infections in Egypt.

In Egypt, HCV prevalence rates reach 13% of the population; about 12 million Egyptians of whom around 8 million people are living with chronic hepatitis C without or with cirrhosis **(Kamal et al., 2018).**

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. **(Idele et al., 2014).**

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 **(Smith et al., 2014).**

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, is strongly associated with reduced risk of liver-related morbidity and mortality such as HCC or liver transplantation **(El Khoury et al., 2012)**.

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, flu-like symptoms (e.g., fever, chills, headaches, arthralgia, and myalgia), neuropsychiatric disorders (e.g., severe fatigue, irritability, and apathy), neurological side effects (e.g., seizures, parathesias, confusion, aphasia, cortical blindness, delirium, and extrapyramidal syndromes marked by ataxia), and autoimmune syndromes **(Manns et al.,2014),** Complex drug interactions, and limited efficacy with SVR rates of 20%–29% in patients with HCV genotype 1 infection **(Sulkowski et al., 2013).**

The development of pegIFN-free oral regimens of direct-acting antivirals (DAAs) greatly improved the efficacy and tolerability of HCV treatment in coinfection. 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-coinfected patients treated with a wide range of cART, **(Wyles et al., 2016).**

Aim of the Work

The aim of this study is to evaluate the safety and efficacy of DAAs (sofosbuvir & daclatasvir) in ttreatment of chronic HCV in HCV-HIV co-infected Egyptian patients.

Patients and Methods

I-Technical design:
Type of the study: Observational study.
Study period: 6 months.
Site of the study: Abbasia Fever Hospital.
Sample size: 18 cases
Subjects:
Inclusion criteria:
Age > 18 ys.
HCV RNA positive.
HIV infection confirmed by western blot.
Exclusion Criteria:
Child C cirrhotic patients.
Platelet count < 50000/ mm.
Patients with HCC.
Advanced HIV disease (CD4 < 200).
Pregnancy.
Uncontrolled Diabetes Mellitus (HbA1c > 9%).

II. Operational design:
Process :
Elligible Patients will receive 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 will be 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 asses 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.
- CD4 count.
Steps of performance:
•Complete history taking
•Full clinical examination
•Analysis of the results
•Laboratory data before treatment would be compared with those done during & after treatment
•Preparing conclusions and recommendations

RESULTS

Table (1): Distribution of the studied patients according to demographic characteristics:

	Mean ± SD	**Range**
Age (years)	32.89 ±8.16	21 – 46
	N	**%**
Gender:		
• Male • Female	14 4	77.8 22.2
Marital status:		
• Single • Married • Divorced	7 9 2	38.9 50 11.1
Occupation:		
• Not working • Working	5 13	27.8 72.2
Special habits:		
• No • Smoking only • IV drug abuser only • Both	5 1 1 11	27.8 5.6 5.6 61

The studied patients' age ranged from 21nto 46 years old with mean age 32.89 years. 77.8% of the studied patients were males. Half of them were married and 72.2% were working. More than 60% of them were smokers and addicted to IV substances.

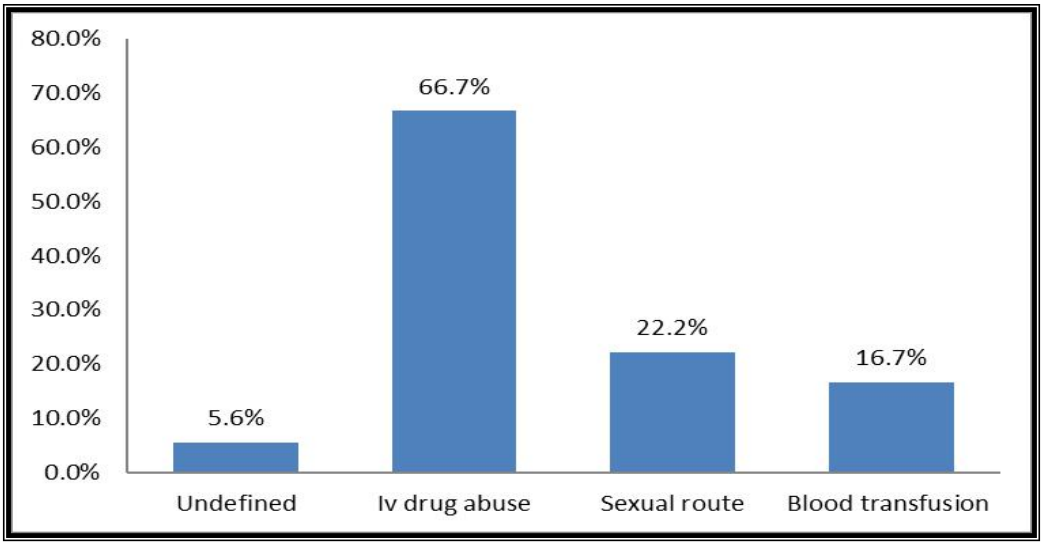
Table (2): Distribution of the studied patients according to their antiviral medication for hepatitis C and HIV infection and HIV PCR

	N (18)	**%**
DAA for HCV:		

• Dual • Triple	15 3	83.3 16.7
Anti HIV agents:		
• Truvada + Efavirenz • Lamivudine+Efavirenz	16 2	88.9 11.1
HIV PCR:		
• <50 • >50	12 6	66.7 33.3

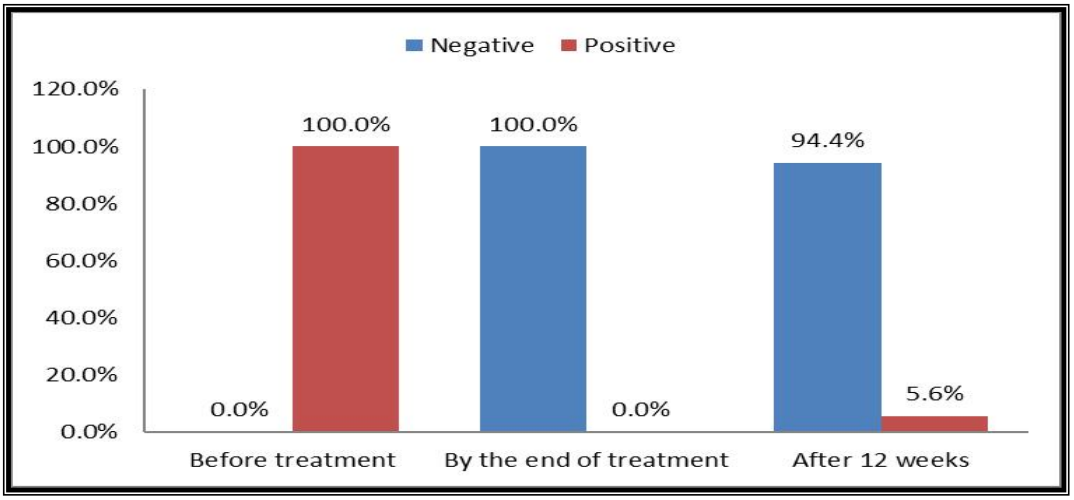
About 83% of the studied patients were eligible to dual therapy protocol of sovosbuvir and daclatasvir. About 89% of them used Truvada & Efavirenz as anti HIV medications, regarding HIV PPCR, two thirds of the studied patients had its level <50.

Figure (1): Simple bar chart showing distribution of the studied patients according to potential route by which they acquire HIV infection.



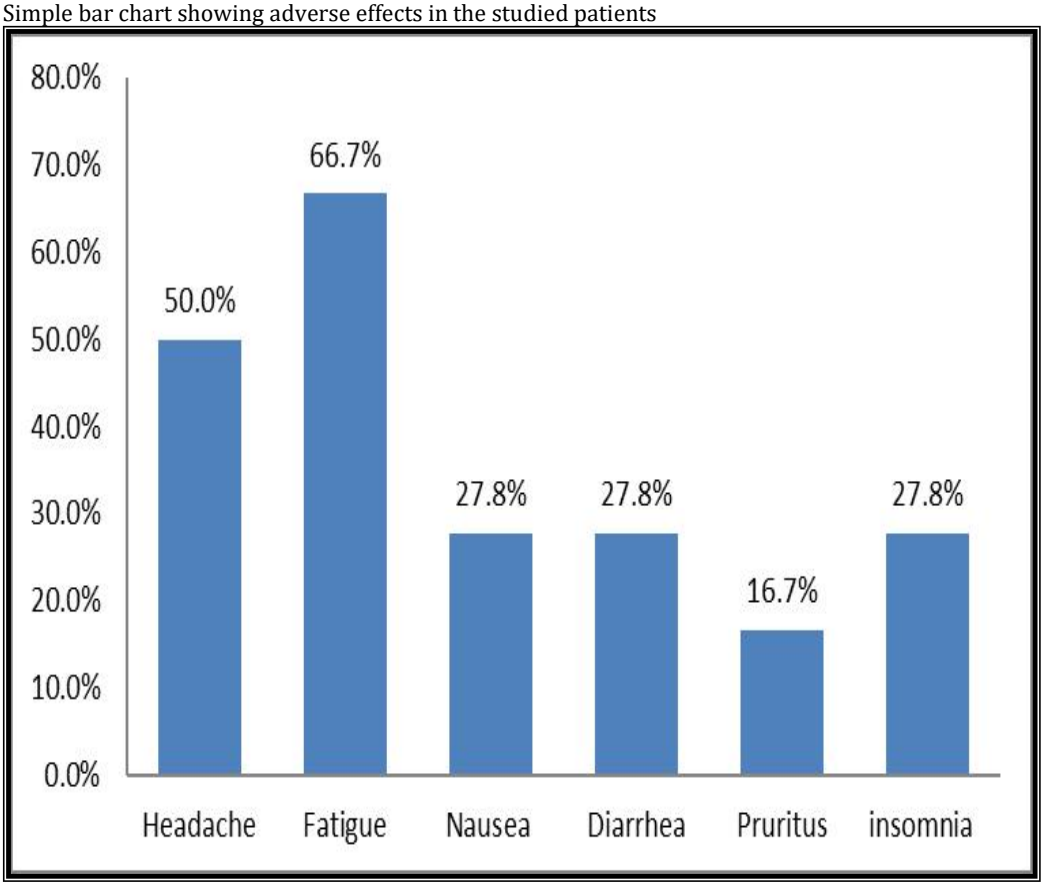
The studied patients had more than one potential risk incriminated in HIV infection including IV drug abuse in 66.7% of them. Slight less than one quarter of them had sexual routes ranging from catching infection from husband to homosexuality and multiple sexual relationships.

Figure (2): Combined bar chart showing PCR HCV among the studied patients before, by the end of treatment and after 12 weeks



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 risky 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).

Figure (3): Simple bar chart showing adverse effects in the studied patients



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).

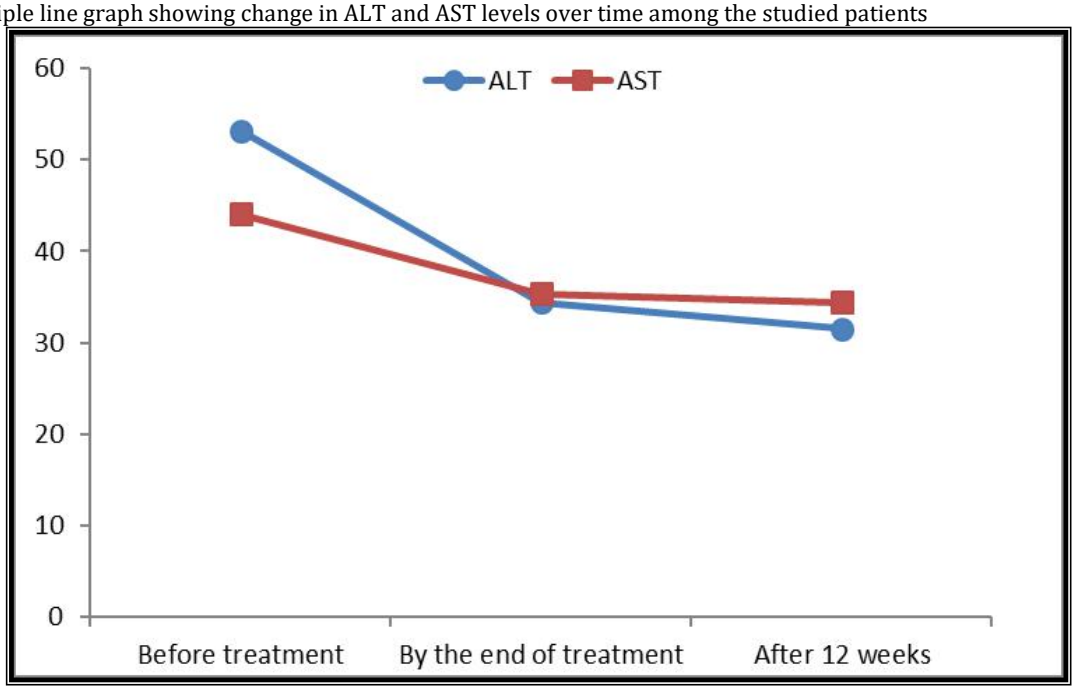
Table (3): Change in CD4 over time among the studied patients:

CD4	Before	By the end of treatment	After 12 weeks	Fr	p
Mean ± SD Median	337.3 ± 158.7 338	354.4 ± 164.5 343	372.4±170.5 360.5	28.44	<0.001**

Fr Friedman test
*p<0.05 is statistically significant
**p≤0.001 is statistically highly significant

There is statistically significant increase in CD4 levels over time. On pairwise comparison, the difference is significant between CD4 levels at any time.

(4): Multiple line graph showing change in ALT and AST levels over time among the studied patients



There is significant decrease in ALT and AST over time in the studied patients. On pairwise comparison, there is significant between ALT levels before and 12 weeks after treatment.

Table (5): Relation between incidence of results of HIV PCR, and studied laboratory parameters among the studied patients:

Percent change of	PCR for HIV				Z	p
	<50 (12)		≥50 (6)			
	Mean ± SD	Median	Mean ± SD	Median		
CD4	10.39±17.68	4.89	20.47 ± 17.45	18.68	-1.873	0.061
Hemoglobin	1.4 ± 4.8	0.36	0.43 ± 1.39	0.78	-0.281	0.779
TLC	-0.32±12.17	4.78	-0.19±25.48	11.32	-0.937	0.349
Platelet count	6.75±14.53	3.13	4.34±3.88	3.38	-0.375	0.708
ALT	33.32±22.05	34.06	22.89±19.62	23.24	-1.124	0.261
AST	19.35±17.42	15.08	9.23± 22.07	7.85	-1.218	0.223
Serum albumin	-0.09±6.1	-2.2	-3.76 ± 4.59	-4.65	-1.079	0.281
AFP	54.07±113.7	30.95	11.98 ± 33.73	10.72	-0.468	0.64
Total bilirubin	13.39±25.71	12.5	4.45 ± 19.15	5.56	-0.565	0.572
Serum creatinine	14.51±18.63	12.5	-3.77 ± 10.01	-4.17	-2.286	0.022*
PT	4.24 ± 4.16	3.04	1.69 ± 2.17	1.54	-1.218	0.223
INR	9.75 ± 6.49	8.71	7.02 ± 5.8	8.18	0.997	0.319
RBS	0.62±11.43	-2.31	2.15 ± 7.09	1.59	-0.656	0.512

*p<0.05 is statistically significant Z Mann Whitney test.

There is statistically significant difference in percent change in serum creatinine over 6 months among patients with different HIV PCR.

There is statistically non-significant difference between patients with different HIV PCR levels and percent change in any other of the above mentioned laboratory parameters.

DISCUSSION

According to The Joint United Nations Programme on HIV/AIDS (UNAIDS) fact sheet, 2015, globally about 36.9 million (34.3 million–41.4 million) people are living with HIV and approximately five million people are co-infected with HIV and HCV.

In Egypt, HCV prevalence rates reach 13% of the population; about 12 million Egyptians of whom around 8

million people are living with chronic hepatitis C without or with cirrhosis **(Kamal et al., 2018).**

With the widespread use of antiretroviral therapy, HIV infection is viewed by many as a chronic disease, with significant improvements in AIDS-related mortality; however 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 **(Smith et al., 2014).**

Treatment of HCV with Interferon and Ribavirin with or without the first-generation HCV protease inhibitors in patients who are co-infected with HIV and HCV has historically been associated with low rates of sustained virologic response, high rates of treatment-related cytopenias, and complex interactions with concomitant antiretroviral drugs. The development of interferon-free oral regimens of direct-acting antiviral agents represents an important chance for better HCV treatment in patients with HIV–HCV co-infection **(Sulkowski et al., 2013).**

The combination of daclatasvir and sofosbuvir has been associated with high rates of sustained virologic response and a favorable side-effect profile when administered for 12 weeks or 24 weeks, with or without ribavirin, to the mono-infected patients with HCV **(Sulkowski et al., 2014, Manns et al., 2014, Everson et al., 2014 and Wyles et al., 2015).**

Daclatasvir and sofosbuvir have limited pharmacokinetic interactions with antiretroviral drugs, and dose adjustments for daclatasvir in patients receiving moderate antiretroviral inducers or strong inhibitors of cytochrome P-450 3A4 are straightforward. Thus, this combination may be valuable for treating patients with HIV–HCV co infection **(Bifano et al., 2013).**

The aim of our study is to estimate the efficacy of DAAs in treatment of chronic HCV in patients co-infected with HIV after completion of 12 weeks of daclatasvir plus sofosbuvir for HCV infection.

In current study, an eighteen patients; their age 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 HIV–HCV coinfected 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 (2017).** They found that the SVR 12 in HIV/HCV co-infected patients receiving all oral DAAs regimens (25% were receiving sofosbuvir and daclatsvir combination) was about 91%.

SVR rate of 91% was also reported by **Hezode et al., in (2015)** in a real life study explored the efficacy of daclatasvir plus sofosbuvir, with or without ribavirin, in patients infected with HCV GT-4 mainly.

On the other hand, SVR rate reported in the current study is lower than the high rates observed by **(Wyles et al., 2015)** study and in close approximate to (Omar et al., 2018) study.

Wyles et al., (2015) study revealed SVR rate of 97% when the same combinations of DAAs were evaluated in patients co-infected with HIV and HCV genotype -1 mainly in a close approximate to ours which revealed SVR rate of 94.4%.

Panel et al., (2015) also found that both Daclatasvir and sofosbuvir have limited pharmacokinetic interactions with other antiretroviral drugs; there are 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) were receiving antiretroviral combination of truvada and efavirenz, (2 patients) were receiving antiretroviral combination of: lamivudine and efavirenz. And also there were no drug interactions between DAAs and ARVs.

No modifications in HIV therapy were needed with the receipt of daclatasvir or sofosbuvir during treatment in our study which agrees with the recommendations of **(Garimella, et al., 2016).**

The optimal duration of treatment for cirrhotic patients is unknown; at this time, the recommendations include extension of therapy to 24 weeks **(Pawlotsky et al., 2018, Panel et al., 2015).**

Data in HCV monoinfected patients has suggested that 12 weeks of sofosbuvir plus daclatasvir does not provide adequate efficacy for cirrhotic patients **(Poordad et al., 2015).**

However, in the current study SVR 12 rate in patients with significant liver fibrosis was 94.1% (1\17) in those who completed therapy and follow up.

This goes with ALLY-2 trial which demonstrated that 12 weeks of HCV treatment with sofosbuvir plus daclatasvir was highly efficacious and well tolerated among HIV/ HCV co-infected patients across HCV genotypes 1–4 (predominantly genotype 1), regardless of prior treatment experience and presence of liver cirrhosis, but it should be highlighted that few number of cirrhotic patients were enrolled in both studies **(Wyles et al., 2015).**

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, an early virologic response, previous failure of IFN-based therapy, treatment duration and use of ribavirin **(Ghany et al., 2011**), while in the era of DAAs based therapy, baseline viral load, previous interferon experience, and the use of RBV were reported to do not affect treatment efficacy **(Naggie et al., 2015)** and (**Wyles et al., 2015).** In our study; all the three patients who received RBV with sofosbuvir and daclatasvir have HCV RNA undetected at 12 weeks.

Our results also agreed with (**Wyles et al., in 2015)** in reporting higher relapse rate among patients who had a high baseline HCV RNA level. The threshold for an increased rate of relapse in **(Wyles et al., in 2015**) study (2 million IU per milliliter) was lower than that in the ION-3 study (6 million IU per milliliter); the only relapsed case in our study was (< 14 million IU per millimeter), these discrepancies could be attributed to the fact that serum HCV RNA load is not a stable parameter because it fluctuates **(Zeuzem et al., 2015).**

About the effect of achieving SVR on CD4 count, **Dazley et al., in (2015)** agrees with our study and shows an increase in CD4 count after achieving SVR which explained by regression of liver fibrosis that may lead to the prevention of splenomegaly and cirrhosis as the most relevant potential mechanisms that lead to a higher CD4 count when HIV subjects are treated for HCV and achieve

SVR. Moreover, they described the effect of chronic inflammation in the non-SVR group leading to a depressed CD4 count (i.e., from HCV viremia) as another possible explanation **(Dazley et al., 2015**), another plausible explanation is the persistent immune activation and CD4 T cell apoptosis involved with HCV infection in the co-infected patients **(Braitstein et al., 2009)**. This activation decreases in response to the success of the HCV treatment. This agrees with of the results of our study of significant increase in CD4 count after achieving SVR.

According to **(Elsharkawy et al., 2017; Bachofner et al., 2016)** there is 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 **(Chekuri et al., 2016).** This agrees with our study that shows a significant decrease in ALT and AST over time in the studied patients 12 weeks after the end of treatment.

The daclatasvir plus sofosbuvir combination regimen was well tolerated with no reported serious adverse events and no discontinuations due to adverse events, and the majority of events observed were categorized as mild or moderate as (fatigue 66.7%, headache 50%, nausea and GI upset by 27.8%). There are also no clinically significant chemistry (creatinine, albumin, bilirubin, PT, INR, alpha feto protein) or hematologic (hemoglobin, platelet count, white blood cells count) abnormalities were determined. This was similar to what was reported by **(Sulkowski et al. in 2014 and Naggie et al., in 2015)** about safety of DAAs in HIV/HCV co-infected patients and what was reported by **(Wyles et al., in 2015)** about safety of daclatasvir plus sofosbuvir combination in co-infected patients.

The patient with relapse had an inherited bleeding disorder (hemophilia) which is considered an important risky factor due to contaminated blood products. This happened although the treatment efficacy rate of DAA therapy for patients with inherited bleeding disorders reported to be similar to that of HCV mono infection **(Walsh C et al., 2017; Nagao A et al., 2017).** Another possible explanation of the relapsed case is the high viral load of HCV (< 14 million IU per milliliter) which is linked to higher relapse rate as in **(Wyles et al. in 2015 and Falade-Nwulia et al., 2017).**

The presence of a chronic viremic carrier state with either HCV or HIV has led to the opportunity of viral-induced glomerular injury, including direct viral infection of renal tissue and the development of circulating immune complexes composed of viral antigens that deposit along the glomerular basement membrane **(Kupin, W.L., 2017)** and it was found a favorable impact of SVR on HCV-associated kidney diseases **(Sperati, C.J., 2013).**

Our study is limited by the small sample size, short observation period and all cases were studied in a single center. Since the number of patients with HCV\HIV co infection is relatively small, we need further data on DAA therapy of these patients. A longer observational period is necessary to evaluate the efficacy and safety of DAA therapy and explore their anti-HCC effect.

Conclusion:

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

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