

# HIV Prevalence among HCV Egyptian Infected Patients and Its Impact on the Result of HCV Treatment

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## ABSTRACT

**Background and Aim of the Study:** HCV infection is the most common co-infection in HIV patients so we aimed to determine the prevalence of HIV infection in chronic HCV patients and its impact on chronic HCV patients treatment response. **Patients and Methods:** A retrospective study performed on 1852 chronic HCV patients subjected to anti HCV treatment with alpha 2a, alpha 2b or standard interferon and Ribavirin and tested and confirmed for HIV co infection by ELISA twice. Upon HIV testing, two groups were generated, **Group 1:** 1840 HCV patients, positive for HCV RNA, and **Group 2:** 12 HIV positive patients and positive also for HCV. Informed consents were obtained from patients. Proper hematological biochemical investigations and other causes of hepatitis rather than HCV were carried out and excluded. **Results:** The prevalence of HIV among HCV infected Egyptian patients was 0.64%. We found a male gender predominance; the hematological and biochemical parameters were similar in both groups with mild elevations in liver enzymes in group II. High rates of failure to treatment (77.8%) with lower SVR (22.2%) were in group II compared to group I (59.9%) as SVR was 22.1% in group II vs. 34.1% in group I, however with no statistical significance. **Conclusion:** Despite the lower prevalence of HIV in Egyptian patients with HCV infection, it still affects their response to treatment. Therefore; we must screen HIV in all HCV patients and recommend its test to routine investigations before starting HCV therapy.

**Keywords:** HCV; HIV; Co-Infection; Response; IFN/Ribavirin

## 1. Introduction

The incidence of hepatitis C virus (HCV) is 20% in highly endemic areas, including urban centers and the Nile Delta in Egypt [1]. Egypt has the largest epidemic of hepatitis C in the world. The percentage of Egyptians with HCV is 14.7%. This is ten times greater than any other country in the world. Nearly half live in urban areas. The prevalence of HCV varies throughout the country. The northern Nile Delta appears to have the highest prevalence, ~28%. The much smaller population of Upper Egypt, in the south, seems to have the lowest HCV prevalence, ~16% [2]. Among the six major HCV genotypes found worldwide, genotype 4 is the most predominant in Egypt, with 4a as the dominant subtype [3].

The HIV epidemic has claimed the lives of nearly 30 million persons worldwide, and an estimated 34 million persons currently are living with HIV infection in 2011 [4].

The prevalence of HIV in Egypt is 0.03 among the general population and ranges from 0.05 - 0.5 among people with high risk behavior (in 2009, number of people living with HIV/AIDS was 11,000 (2400 women, <0.1% adults) and number of deaths were <500), so Egypt faces several challenges in maintaining a low prevalence of HIV/AIDS [5].

Infection with HCV is the most common co-infection in people with HIV since both infections share similar routes of transmission [6]. So all HIV-infected persons should be evaluated for chronic HCV infection using a third generation enzyme immunoassay. Patients who are found to be HCV seropositive should undergo quantitative HCV RNA testing in order to confirm the presence of viremia. Patients who are found to be HCV seronegative should undergo HCV RNA testing if they have advanced immune suppression (e.g., CD4 counts < 100 cells/mm<sup>3</sup>), risk factors for HCV infection, or elevated

aminotransferases [7].

We aimed to determine the prevalence of HIV infection in chronic HCV patients and to detect the impact of HCV/HIV co infection on the response to treatment with Peg interferon and Ribavirin in chronic HCV patients.

## 2. Patients and Methods

### 2.1. Study Population

This is a retrospective study which was performed on one thousand eight hundreds and fifty two patients; all of them were attending The Tropical Medicine Department, Outpatient Clinic of Kasr El Aini Cairo University and Kasr El Aini Viral Hepatitis Center & EL Fatemeia hospital during the period from May 2009 to October 2011: all of them were HCV positive patients and they were attending to receive the anti viral therapy in the form of interferon either alpha 2a, alpha 2b or standard interferon and Ribavirin, their sera were examined for HIV by ELISA test and confirmed by ELISA twice to detect the prevalence of HIV among HCV patients and also to detect how co infection HCV/HIV affect their response to interferon and ribavirin therapy.

### 2.2. Study Design

Upon HIV testing for all patients, two groups were generated:

#### Group 1:

Included 1840 HCV patients' with positive anti-HCV antibodies tested by third generation ELISA and positive HCV RNA by PCR; they were 408 (22.2%) females and 1432 (77.8%) males.

#### Group 2:

Included 12 HIV positive patients detected by ELISA test and confirmed by ELISA twice and positive anti-HCV antibodies tested by third generation ELISA and positive HCV RNA by PCR, they were 10 (83.3%) males and 2 (16.7%) females.

#### Inclusion criteria:

- Adult HCV +ve patients of both sexes.
- METAVIR score: A2 and  $\geq$ F1 or  $\geq$ A1 and  $\geq$ F2;
- ALT > 1.5 UNL.
- No prior treatment with any type of IFN and ribavirin.
- Hemoglobin over or equal 11 g/dl, Leucocytes over or equal 3000/mm<sup>3</sup>, Neutrophils over or equal 1500/mm<sup>3</sup>, Platelets over or equal 100,000/mm<sup>3</sup>, Blood creatinine equal or less than 1.5 mg/dl, Normal TSH, Fasting blood sugar between 70 - 115 mg/dl (if glucose intolerance or diabetes: HbA1C  $\leq$  8.5%).
- Normal ophthalmologic examination in patients with history of hypertension and/or diabetes.
- Effective contraception during the treatment period for both sexes.
- No breastfeeding during the treatment period.

#### Exclusion criteria:

- Patients with autoimmune hepatitis.
- Patients with concomitant HBV.
- Patients with drug history, which can elevate liver enzymes.
- Patients with alcoholic hepatitis.
- Pregnant female or any patient planning for pregnancy.

An informed consent was obtained from all patients.

### 2.3. Methods

All patients of both groups (I & II) were subjected to the following:

**Careful history taking and thorough clinical evaluation** with special emphasis on the evidence of liver dysfunction and physical conditions that could be contraindications to treatment.

**Laboratory investigations:** Including urine and stool analysis, CBC, ESR, liver profile: in the form of (ALT, AST, total and direct bilirubin, serum albumin, PC & INR in addition to AFP). Autoimmune profile (ANA & ASMA), TSH level, T3 and T4, Anti Schistosomal Abs; Hepatitis markers HCVAb, HBsAg & HbCAb detected by ELISA; HCV RNA by PCR.

As well as detection of HIV antibody by ELISA test and confirmed by ELISA twice.

**Abdominal ultrasound:** For assessment of the liver, spleen, portal vein, presence of ascites.

**US guided liver biopsy:** Liver biopsies played a central role in the evaluation of chronic HCV patients. Our biopsies were scored according to METAVIR Score [8]. Fibroscan by echo sense was made for some patients.

### 2.4. Statistical Methodology

Quantitative data were presented by mean and standard deviation (SD). They were compared by student's t-test. Non parametric data were presented by Median and Interquartile range (IQR). They were compared by Mann-whitney U test.

Qualitative data were presented by number and percent. They were compared by Chi-square test or Fischer's exact test when appropriate. In all test, *P* value was considered significant if less than 0.05.

## 3. Results

The prevalence of HIV among HCV infected Egyptian patients was 12/1852 (0.66%). The demographic features of the studied groups regarding their age, sex and BMI showed G-I which included 1840 patients, 1432 (77.8%) males and 408 (22.2%) females, their mean age was 40.94  $\pm$  10.182 years and their mean BMI was 28.054  $\pm$  4.3141 and G-II which included 12 patients, 10 (83.3%) males and 2 (16.7%) females, their mean age were 41.89

$\pm 10.142$  years and their mean BMI was  $27.349 \pm 2.9316$ . There was no statistical significant difference between the two groups regarding their gender, age and BMI. By revising the risk factors for specific HIV infection we found risky occupation (tourism), travelling abroad in 2 patients out of the 12 HIV patients. The biochemical parameters between the two studied groups regarding serum albumin, AST, ALT, ALP showed no statistical significant difference as  $P > 0.05$  as shown in **Table 1**.

There was no statistical significance between the studied groups regarding the baseline hematological parameters, clinical or ultrasonographic findings as all were scheduled for anti-viral therapy.

The difference between the two studied groups regarding the quantitative PCR for HCV is shown in **Table 2**. HCV RNA was much higher in group I (HCV only) (though insignificant) as  $p = 0.8$ .

The grades of inflammation of the liver tissue between the two studied groups were illustrated in **Table 3**, 335 patients were with no available data (18.2%) (There were 328 patients with either missing data or they did not do it for administrative or medical reasons and 7 patients did fibroscan), There was no statistical difference between the two studied groups as regard grades of inflammation or stage of fibrosis.

The type of treatment of the studied groups is shown in **Table 4**.

**Group I:** 884 patients (48%) were on interferon alpha 2a, 842 patients (45.8%) were on interferon alpha 2b, 60 patients (3.3%) were on no treatment, 54 patients (2.9%) were on standard interferon.

**Group II:** 8 patients (66.7%) were on interferon alpha 2a, and 4 (33.3%) were on interferon alpha 2b.

So most of the patients of the two groups were on pegylated interferon.

#### Outcome of treatment:

**Failure:** Patients who did not achieve a 2 log<sub>10</sub> drop in HCV RNA by week 12 of treatment [9].

**Relapse:** Patients who had an undetectable viral load at the end of a prior attempt at treatment (end of treatment response) but who did not achieve a sustained virologic response (negative HCV RNA 24 weeks after completing treatment) [9].

**Sustained virological response (SVR):** absence of HCV RNA by polymerase chain reaction six months after stopping treatment [10].

Our patients response to treatment of the two groups was, 1050 patients (56.7%) were dropped out or did not receive treatment, 372 patients (20.1%) showed failure to treatment, 180 patients (9.7%) were under treatment, 39 patients (2.1%) were relapsed after end of treatment, and only 211 patients (11.4%) who reached the sustained virological response.

**Table 5** showed the response to treatment of the two

**Table 1. Biochemical parameters of all the studied patients.**

Biochemical parameters	Group I (HCV only) Mean $\pm$ SD	Group II (HCV/HIV) Mean $\pm$ SD	P value
Albumin (gm/dl)	4.256 $\pm$ 0.4773	4.08 $\pm$ 0.4676	0.296
Total bilirubin (mg/dl)	0.807 $\pm$ 0.3442	0.84 $\pm$ 0.213	0.753
Indirect bilirubin	0.57 $\pm$ 0.274	0.827 $\pm$ 0.32	0.062
AST (Folds)	1.48 $\pm$ 1.372	1.58 $\pm$ 1.088	0.824
ALT (Folds)	1.68 $\pm$ 2.172	2.22 $\pm$ 1.628	0.454
Creatinine (mg/dl)	0.89 $\pm$ 0.198	0.80 $\pm$ 0.200	0.173
Fasting blood sugar (mg/dl)	99.31 $\pm$ 106.62	28.59 $\pm$ 2.93	0.644
AFP (Folds)	0.63 $\pm$ 1.259	1.228 $\pm$ 0.93	0.157
ALP (Folds)	0.706 $\pm$ 2.46	0.59 $\pm$ 0.216	0.890
ANC	3.39 $\pm$ 1.329	3.98 $\pm$ 1.220	0.218
TSH ( $\mu$ U/ml)	1.618 $\pm$ 1.25	1.74 $\pm$ 1.054	0.767

$P > 0.05$  (NS).

**Table 2. PCR of the studied groups.**

HCV RNA $\times 10$	Group I (HCV only)	Group II (HCV/HIV)	P Value
Mean $\pm$ SD	7.86 $\pm$ 29.3	6.03 $\pm$ 9.67	0.86
Median (IQR)	1.26 $\pm$ 4.92	1.93 $\pm$ 8.2	0.0

$P > 0.05$  (NS).

**Table 3. Grades of inflammation and fibrosis of liver biopsies of the studied groups.**

Grade of inflammation	GI	GII	Stages of Fibrosis	GI	GII
Missing			Missing		
No.	335	0	No.	328	0
%	18.2	0.0	%	17.8	0.0
A1			F0		
No.	1046	9	No.	17	0
%	56.8	75.0	%	0.9	0.0
A2			F1		
No.	366	3	No.	945	9
%	19.9	25.0	%	51.4	75.0
A3			F2		
No.	93	0	No.	222	0
%	5.1	0	%	12.1	0.0
			F3		
			No.	249	1
			%	13.5	8.3
			F4		
			No.	79	2
			%	4.3	16.7

**Table 4. Type of treatment of the studied groups.**

Type of treatment	Group I (HCV only)	Group II (HCV/HIV)	Total
<b>No treatment</b>			
Count	60	0	60
Percentage	3.3%	0.0	3.2
<b>Interferon <math>\alpha</math> 2b</b>			
Count	842	4	846
Percentage	45.8%	33.3	45.7
<b>Interferon <math>\alpha</math> 2a</b>			
Count	884	8	892
Percentage	48.0%	66.7	48.2
<b>Standard interferon</b>			
Count	54	0	54
Percentage	2.9%	0.0	2.9

**Table 5. Outcome after exclusion of dropped and pending patients.**

	Group I (HCV only)	Group II (HCV/HIV)
<b>FAILURE</b>		
Count	365	7
Percentage	59.5%	77.8%
<b>SVR</b>		
Count	209	2
Percentage	34.1%	22.2%
<b>RELAPSER</b>		
Count	39	0
Percentage	6.4%	0%

studied groups after exclusion of dropped and pending patients.

**Group I:** 365 patients (59.5%) were considered as failure to treatment, 209 patients (34.1%) achieved the sustained virological response, 39 patients (6.4%) were relapsers to treatment.

**Group II:** 7 patients (77.8%) were considered as failure to treatment and 2 patients (22.2%) achieved the sustained virological response.

Although the failure of treatment in group II (77.8%) was higher than group I (59.5%), but didn't reach a statistical significance.

#### 4. Discussion

In patients with chronic HCV infection, concomitant HIV infection is associated with higher rates of morbidity and mortality related to end-stage liver disease [11].

Liver disease from HCV is now the leading non-AIDS cause of death in the U.S. in co-infected individuals with HIV. Treatment for each disease is complicated, expensive, and has side effects. This presents difficult issues for patients who are living with both HIV and HCV [12].

Egypt has the largest epidemic of hepatitis C in the world. The percentage of Egyptians with HCV is 14.7%. This is ten times greater than any other country in the world [2]. The current population in Egypt is about 78 to 80 million. 14.7% of this population ( $0.147 \times 78$  million) is 11,466,000 persons who have been infected with this virus. That means almost 10% of the total population are infected and are infectious to other people, that is 7.8 million people with chronic active HCV infection. This also is an underestimate because it does not include the number of people who have been infected that are under 15 years of age or over 60 years of age that are chronically infected. The issues of treatments for those that develop HCV related liver disease is essentially a medical care crisis for the country [2].

In the current study The prevalence of HIV among HCV infected Egyptian patients was 12/1852 (0.64%) and this was in agreement with that reported by the National AIDS Control Program (NACP) surveillance in Egypt which revealed that HIV prevalence is 0.03 among the general population and ranges from 0.05 to 0.5 among people with high risk behavior [13].

Unsafe sexual behavior among most population and limited condom use place Egypt at risk. According to the (National AIDS Program), there were 1.155 people living with HIV in Egypt by the end of 2007 [14].

The United States Public Health Service recommended that all patients with HIV must be undergoing testing for HCV [15].

All of the previously mentioned data created the need to screen for HIV in HCV patients in Egypt. So our study was performed on one thousand eight hundreds and fifty two patients.

This study showed that the mean age of group I (HCV only) was  $40.94 \pm 10.182$  years which was similar to study documented by Armstrong *et al.* (2006) [16], who found that HCV prevalence was highest among persons 30 - 49 years old, and accounted for two-thirds of all infections, and lower than average among persons less than 20 and greater than 50 years old.

Our study showed that the mean age of group II (HCV/HIV co infection) was  $41.89 \pm 10.142$  years which was similar to results obtained by International AIDS Society-USA panel (2010) [17], which revealed that the age of distribution for HIV was between 20 - 50 years old.

Our study detected that two patients out of 12 patients of group II (HCV/HIV) co infection had risky occupation (working in tourism), travelling abroad as both HCV and HIV viruses were shared routes of transmission, there were no other specific risk factors for co-infection and this result was similar to CDC in (2005) [18], which reported that about one-quarter of the people infected with HIV also have HCV.

Our results showed that there was a mild elevation in liver enzymes in group I which was similar to results obtained by Chopra *et al.* (2011) [19], who showed that approximately 65 percent of anti-HCV and RIBA-positive individuals with a normal serum ALT are viraemic. The remainder, it is assumed, has either low level viremia (below detectable levels) or resolved infection. Although the serum ALT concentration is within the normal range in these patients at the time of diagnosis, these values may occasionally fluctuate out of the normal range. However, it is unusual for the value to exceed 1.5 times the upper limit of normal.

The reasons why serum ALT concentrations are normal in some patients and elevated in others are not well understood. However, several intriguing associations have been noted such as the age, the female gender, and the immune state of the patients, the viral genotype and the viral load [20].

In the current study there is no significant difference as regard liver enzymes (ALT & AST) between group I & group II as the mechanism of interaction between the two viruses and their impact on liver injury is not completely understood. HCV is not directly cytopathic and the pathogenesis of liver injury is believed to be immune mediated [21]. It can be argued that HIV patients should develop less severe liver injury because of the immune suppression [22].

Our results represented that there were normal hematological parameters in group I (HCV only) which was far from results obtained by Janus *et al.* (2004) [23], who showed that HCV antibody-positive individuals were 3-fold more likely to have low neutrophil counts.

The difference in our results could be explained as our patients were early patients who were chosen from the start with normal Hematological parameters as they were scheduled for interferon therapy, as abnormal hematological parameters patients were excluded from the start until their parameters were corrected.

We found that although there was no statistical significant difference in HCV viremia in patients with HCV alone compared with HCV/HIV co-infected patients, HCV RNA was much higher numerically in G I patients than G II patients.

These results were different from the results that were obtained by Mehta *et al.* (2002) [24], who showed that patients with HIV infection are more likely to have HCV viremia compared with those without HIV infection. They explained that as clearance of HCV was less likely to occur in patients with underlying HIV.

Also during the chronic stage of either HIV or HCV infection, a relatively stable viral load or "set point" is maintained. However, in the setting of combined infection, HCV RNA levels increase after HIV seroconversion and continue to increase over time compared with pa-

tients with HCV alone. The level of HCV viremia is inversely correlated with lower CD4 counts in most, but not all studies [25] and may transiently increase with initiation of antiretroviral therapy (ART) or heavy alcohol use [26].

The lower level of viremia in the combined infection (HCV/HIV) in our study could be explained by the relatively small number of patients in group II.

There was no statistical significant difference detected in the fibrosis progression in patients with HCV alone compared with HCV/HIV co-infected patients in our study and this went hand in hand with Sterling *et al.* (2010) [27], who found that HIV status was not associated with increased necroinflammatory activity or fibrosis compared with patients with HCV alone. A possible explanation for these discrepant findings may be related to varying degrees of immune suppression in these patients.

In contrast Kim *et al.* (2009) [28], found that HIV/HCV-co infected patients have accelerated rates of fibrosis progression compared with patients with HCV alone, which may be related to HIV-associated immune activation, CD4 T cell depletion or immunodysregulation with production of pro inflammatory cytokines.

Our study showed that all HCV/HIV co infected patients and most of the HCV alone patients were on Pegylated interferon and ribavirin. This was similar to Chopra *et al.* (2011) [19], who recommended for patients with genotype 2, 3 or 4 who were candidates for therapy, treatment with peginterferon and Ribavirin rather than treating with standard interferon and ribavirin or peginterferon monotherapy.

Also the results of (APRICOT) AIDS PEGASYS Ribavirin International Co infection Trial obtained by Carrat *et al.* (2004) [29], were similar to our regimen of treatment which showed that treatment with Pegylated interferon and Ribavirin combination therapy has significantly improved overall SVR rates to more than 55% in patients with HCV alone compared with earlier rates of approximately 35% achieved with standard therapy.

The clinical outcomes of The RIBAVIC trial obtained by Carrat *et al.* (2004) [29] (A randomized, controlled trial of PEG-interferone-alpha-2b plus ribavirin vs interferon—alpha-2b plus ribavirin for chronic hepatitis C virus infection in HIV-co-infected persons) which included 412 patients also supported the superiority of pegylated interferon/Ribavirin versus standard interferon/Ribavirin combination therapy for the treatment of HIV/HCV co infected patients.

Our work showed that there were 209 patients (34.1%) among G I who achieved the SVR while two patients (22.2%) of G II achieved the SVR. Our results were similar to results obtained by Shire *et al.* (2007) [30], who showed that rates of SVR appear to be lower in HIV/

HCV-co infected patients than in patients with HCV alone, in patients with HCV mono infection, overall treatment response rates to pegylated interferon/Ribavirin therapy approach 55%; however, overall response rates in HIV/HCV-co-infected patients are approximately 35%.

Our results were similar to the results obtained by Bardley H (2006) [31], who showed that in 479 co infected HCV/HIV patients, 29.6% had sustained virologic response and 70.3% did not.

We found that there were high rates of dropping from treatment 1050 patients (56.69%) which was similar to the results of the RIBAVIC trial detected by Carrat *et al.* (2004) [29], as treatment discontinuation occurred in 42% of the patients overall due to severe side effects which occurred in 31% of patients. The results reported were based on an intent-to-treat analysis.

This study suggested that there may be qualitative differences in treatment efficacy between HIV/HCV-co infected patients compared to those with HCV infection alone.

The differences in the result can be explained in many ways as the difference between the genotypes of the virus of our patients and patients of other studies. Individuals infected with HCV genotype 2, 3 have better response than HCV genotypes 1, 4 "like the situation in Egypt, where genotype 4 is predominant" [13-32]. Also the number of HIV patients included in our study was too small to draw definitive conclusions.

The limitation of the current study was that the number of diagnosed HIV patients among the studied patients was too small and cannot influence the real prevalence of HIV among Egyptians.

## 5. Conclusion

Patients with combined infection HCV/HIV have a higher rate of failure to treatment with lower SVR when compared to those with HCV infection only. Therefore, despite of the lower prevalence of HIV in Egypt we must screen HIV presence in all HCV patients and to add its test to routine investigation before starting HCV therapy. Also all HIV-infected persons should be screened for HCV infection.

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