Coinfection of Hepatitis C Virus with Human Immunodeficiency Virus: Not the End of the Story: A Multicenter Egyptian Study

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Background and Aim of the study: HCV infection affects about 30% of HIV-positive individuals. Most people agree that HIV accelerates the progression of chronic liver diseases caused by HCV. On other hand there is a lack of clarity regarding how HCV affects HIV infection and disease progression. the study was carried out to evaluate the impact of HCV coinfection on HIV Egyptian patients as regard progress of the disease, response to therapy, comorbid conditions and mortality rates

Patients and Methods: This study was medical record based for 2 years as a multicenter retrospective Cohort study that compared 67 patients of HIV & HCV coinfection with 219 patients of HIV infection .

Results: HIV infection and HIV&HCV coinfection are more common in male than female, the common mode of HIV infection were , heterosexual, homosexual, and drug users, with no significant difference between the two groups. There was a statistically significant difference between the two groups regarding the AST level and the mean baseline CD4 level. There is no difference between 2 groups as regard response to antiretroviral treatment. The percentage of change in the CD4 level was statistically significantly higher in the HIV group, after treatment. No statistically significant difference between the two groups regarding the overall survival analysis. Increased ALT level, basal CD4 level, and adherence to treatment were shown as independent predictors for negative PCR-HIV.

Conclusion: HIV has no effect on treatment of HCV infection while HCV infection has negative impacts on HIV patients' ability to recover their CD4 cells .

INTRODUCTION

Worldwide, 33.3 million individuals are infected with HIV. Hepatitis C (HCV) infection affects 20–30% of HIV patients, according to estimates. The blood-borne route is the primary route of HCV transmission, which accounts for the high frequency of HIV/HCV co-infection among IV drug users. The danger of transmitting HCV through percutaneous route is ten times greater than the risk of transmitting HIV [1].

Egypt was known to have the highest prevalence of HCV infection in the healthy population in the world at 13.9% in the past century. Approximately 15% - 25% are found in rural communities. An estimated 9.8% of Egyptians suffer from chronic HCV infection [2]. According to the 2008 Demographic and Health Survey, 1 in 10 Egyptians between the ages of 15 and 59 had chronic HCV infection, and 15% of the adult population of Egypt had antibodies to HCV (seropositive), and According to a second survey conducted in 2015, 7% of Egyptians between the ages of 19 and 65 were seropositive to HCV [3].

Due to their great effectiveness and safety, DAAs have recently been included to HCV infection regimens both internationally and in Egypt.

This has improved the prognosis of HCV-infected patients and reduced complications [4].

HCV is non-cytopathic in nature and does not integrate with the host genome. Liver damage resulting from HCV infection is caused by a reaction cascade triggered by host defense mechanism against HCV-related substances. To combat the viral onset, both innate and adaptive immunity are stimulated. The cell-mediated immune response involving CD4+ Th1 cells and CD8+ cytotoxic T-lymphocyte (CTL) cells was discovered to have a significant role in generating liver damage during the establishment of host immunity [5].

About 11,000 those are presently living with HIV in Egypt, according to UN AIDS (2016) figures. According to the Ministry of Health and Population (MHP), more than 13000 Egyptians was estimated to be HIV/AIDS positive in 2020. Egypt has a low HIV prevalence, with less than 0.1 % of the population being HIV positive. [6].

Because HCV is a blood-borne virus that is transmitted through direct contact with the blood of an infected person, HIV and HCV coinfection is common (62%–80%) among HIV-infected injecting drug users [7].

The indication for HCV therapy, particularly in those who have co-infected with HIV, has been enhanced due to direct-acting antivirals (DDA), which exhibit higher antiviral efficacy, less side effects, pangenotypic action, and are co-formulated. It is often preferable to begin dual therapy concurrently by sequentially initiating antiretroviral (ARV) and then DAA as fast as possible [8].

In patients with HIV infection, viral coinfections are frequently observed, especially in those who have contracted HIV through a common pathway some of those co-infections may go unnoticed and have little to no effect on the HIV disease or persons who have it. In contrast, HIV co-infection with certain viral illnesses can alter the course of HIV infection naturally and vice versa. When co-infecting the same host, some infectious agents, such as HCV, HBV, human T-cell lymphotropic virus-1 (HTLV-1), human herpes virus-8 (HHV-8), and human papilloma virus (HPV), can alter both their own natural histories and the course of HIV infection and illness [9].

PATIENTS AND METHODS

Study design: this is multicenter retrospective cohort study based on 2 years of medical records.

Study settings: This study was carried out in Department of Tropical Medicine (Mansoura University- Egypt), Mansoura fever hospital, and El-Mahalla El-Kubra fever hospital, between January 2018 and January 2020. Mansoura University Hospital is a tertiary referral center in the Delta of Egypt, patients attending this hospital belongs to the Dakahlia, Damietta, and Port Said. While Mansoura fever hospital, and El-Mahalla El-Kubra fever hospital, are centers for HIV patient treatment for more than 3 governorates Dakahlia, Gharbia, Damietta and other governorates

Study patients: consecutive patients with HIV infection for group I and also consecutive patients with HIV& HCV coinfection for group II were included in this study.

Endpoints:

The primary end-point of this study is to fulfill adequate number of patients participated in both groups in this study and met the inclusion criteria based on medical record.

Secondary end-points

Feasibility of HCV impact on HIV patients and vice versa

Sample size

Sample calculation: We assume that the HCV positive antibody prevalence is 10% according to the last Egyptian HCV Health Survey [3] , HIV prevalence was about 0.1%. [6] and HCV prevalence among HIV patient was about 20-30% [1]. To provide approximately 95% power, 0.05 alpha level and, ratio $(n2/n1) = 3$, based on that the prevalence of HCV among HIV patient was about is approximately one third. The calculated sample size was about 311 Participants depend on that we started by 400 patients as following: 300 consecutive patients with HIV infection for group I and 100 consecutive patients with HIV & HCV coinfection for group II, all patients must fulfill all following criteria.

Inclusion criteria:

1- Adult patients above 18 years old

2- +VE PCR for HCV and HIV in group I

3- +VE PCR for HIV in group II

4- Medical records that contain all required data.

Then we had excluded any of these criteria:

Exclusion criteria:

1- Medical records that missing any required necessary data.

2- Any patient died or loss of follow up (did not follow up the routine hospital visits) for three months before January 2018.

3- Unclear handwritten medical record.

4- Other viral hepatitis infections (HAV- HBV- HDV- HEV).

5- Human T-cell lymphotropic virus-1 (HTLV-1), human herpes virus-8 (HHV-8), and human papilloma virus (HPV)

Finally the study was conducted on two groups: (Group I): HIV group included 219 medical records for patients of human immunodeficiency virus infection. (Group II): HIV-HCV group included 67 medical records for patients with coinfection with hepatitis C virus and human immunodeficiency virus.

Patient assessment:

After taking the all ethical consideration, the following data were collected from medical record of patients under the study:

1. **Socio-demographic data and full history taking:**

   Personal history data (age, sex, residence, and special habits)

2.   **Full clinical data and examination.**

3.   **Laboratory data:**

   • Complete blood count.

   • Liver enzymes.

   •Serum creatinine.

   • Hepatitis viral markers for excluding (HAV- HBV- HDV- HEV).

   • Polymerase Chain Reaction for hepatitis C virus.

   • Polymerase Chain Reaction for human immunodeficiency virus.

   • Cluster of differentiation 4 count.

4.   **Treatment and follow up data.**

5.   **Co-morbidity data.**

6.   **Drug-drug interaction data.**

7.   **Complications data.**

8.   **Death and its cause if possible.**

Definitions of diagnostic and therapeutic protocols:

The first step in hepatitis C evaluation is often blood work to check for HCV antibodies using an enzyme immunoassay. If this test shows positive results, hens PCR for HCV must be carried out to confirm the results of the immunoassay and ascertain the viral load [10].

This study diagnostic protocol was depending on MOHP HIV Testing Protocol: an ELISA test is conducted, and a Western blot is conducted as a confirmation test followed by PCR HIV [11].

This study therapeutic protocol was depending on recommendations updates on first- and second-line antiretroviral regimens WHO; 2018 As the ideal first-line antiretroviral therapy (ART) regimen for adults and adolescents, tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) (or emtricitabine, FTC) + efavirenz (EFV) was suggested in guidelines on the use of antiretroviral (ARV) medications for treating and preventing HIV infection. Since then, dolutegravir (DTG) has been used in first- and second-line ART with growing amounts of scientific evidence and programmatic experience [12].

According to the EASL (European association for the study of the liver) and National Committee for Control of Viral Hepatitis (NCCVH) guidelines for HCV therapy Patients with HCV (genotype IV) infections received SOF (400 mg) once daily and DCV 90 mg daily (one day 60mg tablet twice and next day once and so on….) for a period of 12 weeks [13]. According to The initial antiretroviral (ARV) regimens advised for the majority of patients with HCV/HIV coinfection are identical to those advised for HIV-positive individuals without HCV infection [14]. Quantitative and qualitative PCR tests are used with the start of treatment and its follow-up among ART users, detectable plasma HIV-1 RNA levels at the cutoff of 50 copies/ml [14].

Statistical analysis

Statistical analysis of the data was done by using Statistical Package for Social Science (SPSS) version 25.0 was applied for data analysis in the present study. The hypothesis will be tested by comparison the two groups using Fisher's exact test and Chi-square to compare two category variables. Using independent x2 tests, the Hardy-Weinberg equilibrium (HWE) of each group was assessed. The continuous data (age), will be described by mean ± (SD). The binary data (the outcome, exposure, and, potential risk factors), will be described by frequency and percentage. Nonparametric data was presented by median (min-max) with mann-whitney test for significance. The log rank test was used to test the one part of null hypothesis that was no difference in survival between two independent groups (Group I: HIV group and Group II: HIV-HCV group). Univariate and multivariate logistic regression was used to test many variables to determine which of treatment response to HAAR. P < 0.05 was considered to be statistically significant.

RESULTS:

Study participants

Two hundred eighty-six patients joined this study out of the four hundred who fulfilled the inclusion criteria and were initially registered. Ninety-three participants served as exclusion criteria at baseline, thus three hundred and seven patients remaining in this study. We note that 21 patients can't be contacted within 3 months, 17 patient considered as early loss of follow-up and 3 patients were died as displayed in **Figure (1).** The mean age of the cases in the HIV group was 39.9 ± 8.7 years while the mean age in the combined HIV+HCV group was 42.8 ± 11.4 years with no statistically significant difference between the two groups, the majority of the patients in the two study groups were males, HIV group was 63.9% while the combined HIV+HCV group was 74.6%, with no statistically significant difference between the two groups, in addition there was no statistically significant difference between the two study groups as regards of residence, DM, HTN, TB and CMV infections, cirrhosis, and malignancy. As shown in **(table 1).**

Multivariable and Univariate Cox Regression analysis were done for all HIV patients for

predicting high treatment response within the Two Years Follow-Up Period

The Multivariable and Univariate Cox regression analysis show that, increased ALT level, increased basal CD4 level, and adherence to treatment were shown as dependent and independents predictors for negative PCR, as shown in **(table 2).**

Comparison of biochemical data among HIV and HIV+HCV groups

Regardig the laboratory analysis, there was no statistically significant difference between the two study groups as regards of hemogloin level, platelets count, TLC count, level of ALT, serum creatinine and baseline HIV as detected by PCR. There was a statistically significant difference between the two groups regarding the AST level. The mean baseline CD4 level in the HIV group was 413.8 ± 148.7 while the mean level in the combined HIV+HCV was 276.8 ± 132.7, the mean level was statistically significantly higher in the HIV group, as shown in **(table 3).**

Therapeutic Findings

Data for two years observation of 3 regiments as therapeutic deferent lines were available for 286 patients 1st scheme of ART by combination of tenofovir (TDF), emtricitabine (FTC), and efavirenz (EFV) was conducted in 268 patients, 2nd scheme of ART by combination of tenofovir (TDF), emtricitabine (FTC), and dolutegravir (DTG) were conducted in 5 patients, and 3rd scheme of ART by combination of lamivudine (3TC), Azidovodine (AZT), and lopinavir/ritonavir (LPV/r) were conducted in 13 patients. We fouund that there was no statistically significant difference between two groups regarding the drug therapy.The highest percentage in the two study groups used combination of TDF/FTC/EFV and represented 94.5% and 91% in the HIV group and combined HIV+HCV group, as shown in **(table 4).**

The cases in the two study groups were adherent to treatment and represented 99.1% and 95.5% in the HIV group and combined HIV+HCV group respectively with no statistically significant difference between the two groups. The CD4 level after treatment in the HIV group was 600.4 ± 156.7 while the mean level in the combined HIV+HCV was 386.6 ± 163.8, the mean level was statistically highly significantly increase in the HIV group. The percentage of change in the CD4 level was statistically significantly higher in

the HIV group. After treatment, HIV was positive by PCR in 1.8% and 4.5% in the HIV group and combined HIV+HCV group respectively with no statistically significant difference between the two groups, as shown in **(table 5).**

There was no statistically significant difference between the two groups regarding the incidence of mortality. Only 9 cases died in the two study groups; 8 cases in HIV group and 1 case only in the combined HIV+HCV group The causes of death ordered by higher incidence were Opportunistic infection, suicide and IRIS, there was no statistically significant difference between the two groups regarding the overall survival after 24 months and represented 94.1% and 92.5% in the HIV group and combined HIV+HCV group respectively, as shown in **(table 6)** and **(figure 2).**
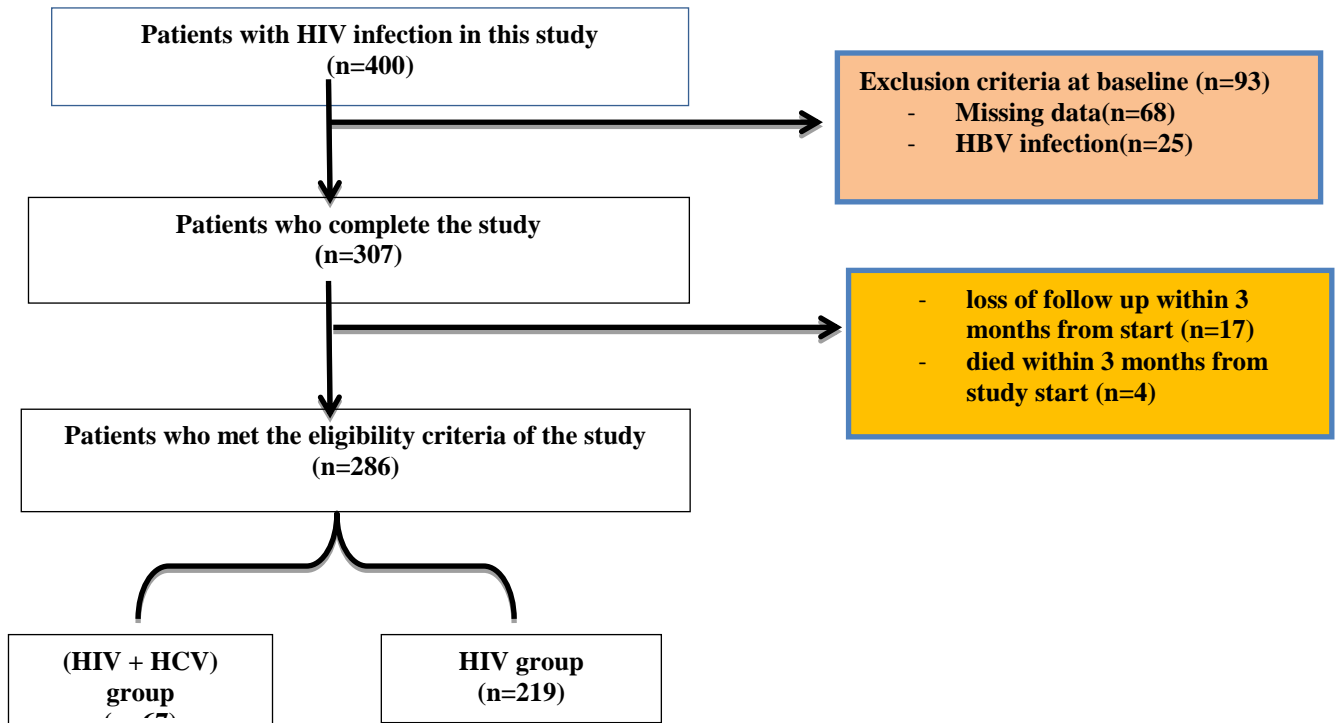

Figure 1: Flowchart of the patients included in this study.

Table 1: Comparison of demographic and clinical data among HIV and HIV+HCV groups.

		HIV (219)	HIV+HCV (67)	P
Age (years) Mean ± SD		39.9 ± 8.7	42.8 ± 11.4	**0.06**
Gender	Male	140 (63.9%)	50 (74.6%)	**0.09**
	Female	79 (36.1%)	17 (25.4%)	
Residence	Rural	128 (58.4%)	43 (64.2%)	**0.4**
	Urban	91(41.6%)	24 (35.8%)	
Cirrhosis		0 (0%)	1 (1.5%)	**0.2**
Diabetes		7 (3.2%)	3 (4.5%)	**0.7**
HTN		7 (3.2%)	2 (3%)	**1**
TB		1 (0.5%)	0 (0%)	**1**
CMV		2 (0.9%)	0 (0%)	**1**
Malignancy		0 (0%)	0 (0%)	**-**

HTN, hypertension; TB, Tuberculosis; CMV, Cytomegalovirus

Table 2: Predictors of negative HIV PCR after treatment with HAART.

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.99 (0.94 – 1.06)	0.97	1.04 (0.91 – 1.18)	0.6
Gender	1.12 (0.3 – 3.9)	0.86	0.44 (0.44 – 4.46)	0.5
HB	1.29 (0.86 – 1.94)	0.2	1.67 (0.63 – 4.45)	0.3
PLT	1 (0.99 – 1.01)	0.96	1.01 (0.99 – 1.03)	0.4
TLC	0.8 (0.6 – 1.2)	0.3	0.57(0.25 – 1.28)	0.2
AST	0.99 (0.98 – 1)	0.3	1.07 (0.98 – 1.16)	0.14
ALT	0.98 (0.97 – 99)	0.004	0.9 (0.83 – 0.998)	0.04
Creatinine	0.09 (0.003 – 2.4)	0.2	0.04 (0.0001 – 15.6)	0.3
Basal CD4	1.005 (1 – 1.009)	0.03	1.01 (1.001 – 1.02)	0.04
CD4 change rate/12M	0.99 (0.97 – 1.02)	0.8	1.01 (0.98 – 1.04)	0.5
Basal HIV PCR	1 (1-1)	0.7	1 (1 – 1)	0.2
Adherence of treatment	60 (8.9 – 414)	< 0.0001	1463 (12.7 – 168799)	0.003

HB; Hemoglobin, PLTs; Platelets, TLC; Total Leukocyte Count, ALT; Alanine transaminase, AST; Aspartate transaminase, CD4; cluster of differentiation 4, HIV; human immunodeficiency virus, PCR; Polymerase chain reaction

Table 3: Comparison of biochemical data among HIV and HIV+HCV groups.

	HIV (219)	HIV+HCV (67)	P
Hb (gm/dl)	12 (7.3 – 16.8)	12.1 (7.5 – 16)	**0.6**
PLT (10^3 /cmm)	247.8 ± 60.7	250.7 ± 56.4	**0.7**
TLC (10^3 /cmm)	5.14 (3.2 – 10.2)	5.19 (3 – 9.7)	**0.8**
AST (U/L)	24 (10 – 180)	29 (11 – 82)	**0.02**
ALT (U/L)	23 (10 -111)	25 (10 – 56)	**0.3**
Creatinine (mg/dl)	0.9 (0.5 -1.3)	0.9 (0.5 – 1.4)	**0.5**
Baseline CD4 (count)	413.8 ± 148.7	276.8 ± 132.7	**<0.0001**
Baseline HIV-PCR(copies/mL)	66029 (1118 – 34089637)	69145 (1118 – 2085710)	**0.7**

HB; Hemoglobin, PLTs; Platelets, TLC; Total Leukocyte Count, HIV-PCR; Polymerase Chain Reaction for HIV

Table 4: Comparison of drug therapy among HIV and HIV+HCV groups.

Treatment regiment	HIV (219)	HIV+HCV (67)	p
TDF/FTC/EFV	207 (94.5%)	61 (91%)	
TDF/FTC/DTG	1 (0.5%)	4 (6%)	**0.13**
3TC/AZT/LPV/R	11 (5%)	2 (3%)	

TDF; tenofovir, FTC; emtricitabine, EFV; efavirenz, DTG; dolutegravir, 3TC; lamivudine, AZT; Azidovodine , LPV/R; lopinavir/ritonavir

Table 5: Comparison of treatment outcome among HIV and HIV + HCV groups

		HIV (219)	HIV+HCV (67)	p
CD4 Count After treatment		600.4 ± 156.7	386.6 ± 163.8	> 0.0001
CD4 Change rate/12M (%)		46 (8 – 222)	38 (11 - 99)	0.01
HIV PCR After treatment	Negative	215 (98.2%)	64 (95.5%)	0.4
	positive	4 (1.8%)	3 (4.5%)	
Adherence to treatment (yes%)		217 (99.1%)	64 (95.5%)	0.09

CD4 Change rate/12M: definition
The CD4 count should begin to rise soon after ART treatment begins. With each year of treatment, the number of CD4 cells tends to increase by count of cells per cubic millimeter (mm3) of blood and also percent.
**Adherence to treatment: definition**
The extent to which patients are able to follow the agreed recommendations for prescribed treatments.

Table 6: Comparison of incidence and cause of mortality with survival analysis among two groups

		HIV (219)	HIV+HCV (67)	p
Mortality	Survived	206 (94.1%)	62 (92.5%)	0.3
	Died	8 (3.7%)	1 (1.5%)	
	Loss of follow-up	5 (2.3%)	4 (6%)	
Cause of Mortality	Opportunistic infection	5 (2.3%)	1 (1.5%)	0.6
	Suicidal	2 (0.9%)	0 (0%)	
	IRIS	1 (0.5%)	0 (0%)	
	loss of follow up	5 (2.3%)	4 (6%)	
Survival more than 24 months		206 (94.1%)	62 (92.5%)	0.4

IRIS; Immune reconstitution inflammatory syndrome
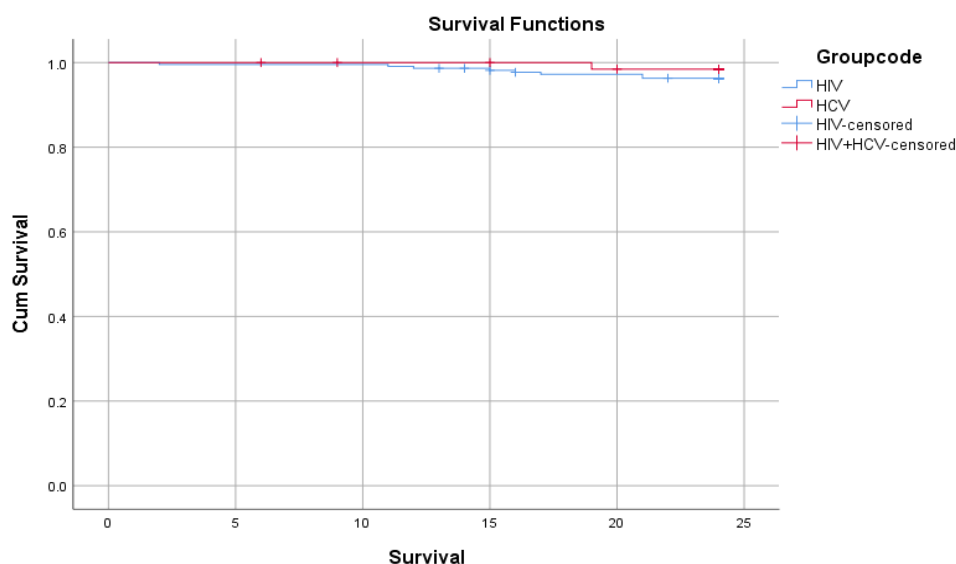
Figure 2: Comparison of survival analysis curve between HIV and HIV+HCV groups.

DISCUSSION

The main aim of this study was describing the HIV-HCV epidemiology with a focus on trends over time appears essential to understand the epidemic at the global level and better target preventive measures especially with the lack of these studies in Egypt.

Therefore, the current study was conducted to highlight the situation of coinfection with hepatitis C virus and human immunodeficiency virus in Egypt as regard progress of the disease, response to therapy, comorbid conditions and Mortality rates.

One of most important finding of our study was that, the increased ALT level, increased basal CD4 level, and adherence to treatment were considered as prognostic factors for HIV treatment outcome according to the Multivariable and Univariate Cox regression analysis; this could be explained as following: Although the exact mechanisms by which HIV damages the liver are still unknown, the most significant ones may involve apoptosis (caused by caspases 2, 7, and 8), mitochondrial dysfunction, and a reduction in mitochondrial DNA in several tissues. HIV proteins may also alter the mitochondrial membrane's permeability, which can also trigger an inflammatory response that lead to elevated liver enzymes [15]. whereas the hepatotoxic effect of HAART drugs as showed in Tesfa et al. 2019 study found that, 9.2% of treatment-unaware controls saw modest liver enzyme elevation, almost 25% of HAART patients experienced mild and severe hepatic enzyme increase, in addition of HCV coinfection hepatotoxicity [16].

The use of HAART has been linked to immune reconstruction. According to the theory, a rise in CD4 cell counts would result in a strong intrahepatic immune response against HCV, most likely because of the rise in CD4 cell population. Sadly, there is little evidence to support the existence of this occurrence. In reality, this topic has been seriously questioned by a number of hypothetical case studies [17]. A quicker rate of immunological success can be attained by starting ART with higher CD4 cell counts. As compared to NVP-containing regimens, efavirenz-containing regimens enhance CD4 cell counts of the patient more quickly when baseline CD4 cell counts are greater. Hence, those with greater baseline CD4 cell counts can start an EFV-containing regimen [18].

In the current study, the mean baseline CD4 level in the HIV group was statistically significantly higher than combined HIV+HCV ($P< 0.01$). This agreed with *Akhtar and his colleagues 2022*, who showed that the mean CD4 count of HIV-HCV coinfected patients was 230 cells/mm3 while in HIV monoinfected patients, the mean CD4 count was raised to 243 cells/mm3 [19]. This is in accordance with a study by *Bhattarai et al., 2018* which showed that HIV patients with CD4+ T cells more than 200 cells/mm3 were 81% less likely to have HIV-HCV co-infection [20]. Similar studies were conducted in Nigeria and India in which the mean CD4 count was reported as 260 cells/mm3 and 288.6 cells/mm3, respectively by *Adewole et al., 2009,* and *Tripathi et al., 2007* [21,22].

In the current study, there was an increase in the CD4 count after treatment compared to before treatment level. The percentage of change in the CD4 level was statistically significantly higher in the HIV group. This matches with *Michienzi et al., 2019* who showed that patients with pre-DAA CD4 levels of less than 350 cells/mm3 show a substantial rise in CD4 count when DAA treatment was used [23]. The current results also came in accordance with *Mohamed, et al 2021*, who reported that obtaining SVR after HCV treatment in HCV-HIV coinfection help in improving CD4 count, treated patients' CD4 counts significantly increased [24].

On the other hand, there was no statistically significant difference between the two study groups regarding hemoglobin level, platelets count, TLC, level of ALT, serum creatinine and baseline HIV as detected by PCR. This came in agreement with *Mohamed, et al 2021*, who reported that there were no statistically significant difference in the CBC, random blood sugar, coagulation profile, or serum creatinine between HIV infection and coinfection [24].

Furthermore, no statistically significant difference existed between the two groups in terms of drug therapy. The highest percentage of the cases in the two study groups used combination of TDF/FTC/EFV and represented 94.5% and 91% in the HIV group and combined HIV+HCV group. This came in accordance with *Akhtar et al., 2022* who reported that All antiretroviral medications were administered in combinations with nucleoside and nonnucleoside

reverse transcriptase inhibitors, however the majority of patients about (38%) were taking tenofovir plus emtricitabine plus efavirenz (TDF + FTC + EFV) **[19].**

As regarding post-treatment results, HIV was positive by PCR in 1.8% and 4.5% in the HIV group and combined HIV+HCV group respectively with no statistically significant difference between the two groups. This came in agreement with *Mohamed, et al 2021*, who showed that Daclatasvir with sofosbuvir with or without ribavirin were administered for 12 weeks to 30 individuals with HIV-HCV coinfections, with a mean age of 33.8 years. At week 12 following therapy, 96.67% of them had a sustained virologic response (SVR 12) **[22].** Also finding matches with *Wyles et al., 2015* study when the same DAA combinations were tested on individuals with co-infections with HIV and HCV, it showed an SVR rate of 97% **[25].**

In patients with HCV genotypes 1 or 4, HIV coinfection impairs the sustained virological response and viral kinetics during pegylated interferon plus ribavirine therapy. However, for the majority of the commonly used direct-acting antiviral medication combinations, the SVR difference between HIV/HCV co-infected and HCV mono-infected individuals has diminished **[26].** However, our findings surpass those of *Milazzo and colleagues' (2017)* and *Hezode et al., 2016* practical applications investigations, which showed that the SVR 12 in HIV/HCV co-infected individuals using antivirals was about 91% SVR. This variation may result from genotypic variation or adherence among patients **[27,28].**

In the current study, there was no statistically significant difference between the two groups as regarding the mortality. Only 9 cases died in the two study groups; 8 cases in HIV group and 1 case only in the combined HIV+HCV group. The causes of death were Opportunistic infection, suicide and IRIS. The overall survival after 24 months and represented 94.1% and 92.5% in the HIV group and combined HIV+HCV group respectively. This agreed with *Mehta et al., 2016* who included 851 patients with HIV and among them, there were 36.9% of cases were infected with HCV. They reported that those without HCV had comparable mortality rates with those who were HIV/HCV uninfected **[29].**

This was in accordance with *Dold et al., 2019* who showed that for both patient groups, the typical observation times were comparable. (HIV 3047 days vs. 3147 days). During the monitoring period, 46 patients overall (14.3%) passed away (HIV infection: 23 (13.1%), HIV/HCV co-infection: 23 (15.8%). The two leading causes of mortality in HIV-mono-infected people were infections (n = 6, of which 4 were not linked to AIDS and 2 were), and cardiovascular disease (n = 6) **[30].** The higher mortality rate in that latter study, as they analyzed the data in case without application of DAAs treatment. The lower rate of mortality was a considerable drop in liver-related mortality has been linked to effective DAA treatment. as find by *Alavi et al., 2019*, and *Butt et al., 2020* **[31,32].**

Antiretroviral therapy does minimize the impact of HIV co-infection on the progression of HCV disease, but it has not yet completely eliminated it, and liver-related mortality is still regarded as the leading cause of death among HIV/HCV co-infected people **[33].**

CONCLUSION

HIV has no effect on response to treatment of HCV infection while HCV infection negatively impacts the patients on HAART's ability to recover their CD4 cells. Increased ALT levels, increased basal CD4 levels, and adherence to treatment may be good predictors of HIV treatment response, but more research with larger patient numbers is required.

Limitations

- Despite that the number of recruited patients was reasonable but not enough for considering the nature of the Egyptian society.
- The main limitation of the current study was the short duration of the study that couldn't reflect the actual course in the disease progression

Ethical consideration: The research gained approval from the local scientific committee and IRB from Mansoura University, also gained

approval from Egyptian Ministry of Health and Population (National AIDS Control Program), and all participants gave informed consent before the onset of this study.

List of abbreviations:
HIV: human immunodeficiency virus
HCV: hepatitis C virus
AST: Aspartate transaminase
ALT: alanine aminotransverase
CD4: cluster of differentiation 4
PCR-HIV: Polymerase Chain Reaction for HIV
HAART: Highly active antiretroviral therapy
DAA: direct-acting antiviral
HCC: Hepatocellular carcinoma
Th1: T helper type 1
CD8: cluster of differentiation 8
CTL: cytotoxic T-lymphocyte
HBV: hepatitis B virus
HTLV-1: human T-cell lymphotropic virus-1
HHV-8: human herpes virus-8
HPV: human papilloma virus
HDV: hepatitis D virus
HEV: hepatitis E virus
MOHP: Ministry of Health and Population
ELISA: enzyme-linked immunosorbent assay
WHO: World Health Organization
ART: antiretroviral therapy
TDF: tenofovir disoproxil fumarate
3TC: lamivudine
FTC: emtricitabine
EFV: efavirenz
ARV: antiretroviral
DTG: dolutegravir
EASL: European association for the study of the liver
NCCVH: National Committee for Control of Viral Hepatitis
SOF: Sofobusvir
DCV: Daclatasvir
HIV-1 RNA: Human immunodeficiency virus type 1-RNA
AIDS: acquired immune deficiency syndrome
AZT: Azidovodine
LPV/r: lopinavir/ritonavir
NVP: Nevirapine
SVR: sustained virologic response

HIGHLIGHTS

- The percentage of change in the CD4 level was statistically significantly higher in the HIV patients than HIV+HCV coinfection.

- The higher basal CD4 level, the higher response to HIV treatment.

- The increased ALT level, may be consider as good prognostic factor for HIV treatment

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