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EFFECT OF HGV ON PATIENTS CO-INFECTED WITH HIV

By

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ABSTRACT

Background: GB virus C (HGV) is classified as pegivirus of the family flaviviridae. It is a positive sense single stranded RNA virus. Due to the shared transmission modes with HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV), co-infection with HGV, are common among people infected with HIV, HBV and/or HCV.

Objective: Determination of the incidence of HGV in chronic liver diseases in frequent blood donors and hemodialysis patients with or without HIV infection and influence of HGV on the course of HIV infection.

Materials and methods: In the present study, 60 patients were divided into 2 equal groups as frequent blood donors group and hemodialysis group. They were mainly between 40 - 60 years old. 10% were females and 90% were males in blood donors group. 26.7% were females and 73.3 % were males in hemodialysis group. They were suffering from chronic liver diseases. They were investigated to study the incidence of HGV in chronic liver diseases with or without HIV infection and influence of HGV on the course of HIV infection. This was in addition to 20 persons who were not exposed to major risk factors of hepatitis as a control group. All members of the study were subjected to complete history and clinical examination as well as laboratory investigations for estimation of CD4 cells count, HBsAg by ELISA, HCV Ab by ELISA, HIV Ab by ELISA and HGV RNA using RT-PCR. Tests of liver functions included serum bilirubin (total and direct), ALT, AST, alkaline phosphatase (ALP), total proteins, and albumin.

Results: Liver biochemical profile showed a significant relations with CD4 cells count where CD4 cells count decreased by increasing of ALT (SGPT), AST (SGOT), alkaline phosphatase (ALP), total bilirubin and increased by increasing serum albumin. Regarding the CD4 cells count and PCR for HGV, patients with HGV have a significant higher CD4 cells count than patients without HGV. Patients with both HIV and HGV have a significant higher CD4 cells count than patients with HIV without HGV. Results indicated that, out of 30 patients of frequent blood donors (BD) group, 28 (93.3%) were negative for HIV, and 2 (6.7%) were positive for HIV. Concerning hemodialysis group (HD), out of 30 patients, 26 (86.7%) were negative for HIV, and 4 (13.3%) were positive for HIV. In case of blood donors group, out of 30 patients, 26 (86.7%) were negative for HGV, and 4 (13.3%) were positive for HGV. Out of 30 patients of hemodialysis group, 26 (86.7%) were negative for HGV, and 4 (13.3%) were positive for HGV.

Conclusions: HGV infection has a moderate frequency among hepatic hemodialysis and frequent blood donors. HIV co-infection with HGV was associated with significantly high CD4 cell count suggesting a beneficial effect of HGV infection on HIV co-infected patients.

Key words: HGV, HIV, CD4 cells count.

INTRODUCTION

Hepatitis virus infection is an increasing problem and millions of humans all over the world are infected. It is accepted as a significant public health problem with several life altering complications. Five viruses are usually associated with hepatitis in humans; hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and hepatitis E virus. In addition to these viruses, there are a number of patients with hepatitis in whom no virus could be identified and it was, therefore, postulated that there might be other agents which might cause hepatitis **(Sehgal and Shama 2002)**. New viruses have been identified for their association with hepatitis. Hepatitis G virus (HGV) is a single stranded RNA virus which represents a newly discovered virus belonging to the flavivirus family. Hepatitis G virus (HGV) and GB virus type C (GBV-C) were independently discovered. However, it was later determined that they were two isolates of the same virus **(Stapleton, 2003).**

HGV can be demonstrated in patients with chronic liver diseases. Epidemiological data indicate that the virus is transmitted via blood/blood products, sexually and vertically from infected mothers to children **(Stapleton, 2003).** Epidemiological data indicate that HGV, like HCV is distributed globally and prevalent among hemodialysis patients **(Okuda *et al.*, 2000).** According to the epidemiological studies, HGV co-infection in HIV seropositive patients is associated with beneficial effects as increasing CD4 cells count which leads to slower disease progression, longer survival after AIDS development, and lower HIV serum viral loads **(Shankar *et al.*, 2008).** The aim of this study was to evaluate HGV infection among chronic liver diseases patients with or without HIV infection, and influence of HGV on the course of HIV infection by assessment of CD4 cell count.

MATERIALS AND METHODS

This work was carried out in the period of 2012 to 2015 in the Cinical Pathology Department, Al-Hussien Hospital, Faculty of Medicine, Al-Azhar University. Serum samples from 60 patients suffering from chronic liver diseases admitted at Al-Hussien hospital, Faculty of Medicine, Al-Azhar University were investigated to this study. This was in addition to 20 persons who were not exposed to major risk factors of hepatitis as a control group. The patients were divided into two main equal groups: group 1 have routine hemodialysis each of them underwent dialysis on specific dialyzer according to the type of virus which he had, and group 2 who were frequent blood donors became chronic hepatitis patients. All members of the study were subjected to complete history and clinical examination as well as laboratory investigations for estimation of CD4 cells count by Dynal Biotech kits according to the manufacturer's instruction that based on the method described by **Crowe *et al.* (2003).** HBsAg by ELISA was estimated using Dialab HBsAg Kit according to the manufacturer's instruction that based on the method described by **Weissman and Krugman (1987).** HCV Ab by ELISA was estimated using Dialab HCV Ab Kit according to the manufacturer's instruction that based on the method described by **Engvall *et al.***

(1971). HIV Ab by ELISA was estimated using Dialab HIV 1&2 Ab Kit according to the manufacturer's instruction that based on the method described by **Barb *et al.* (1994).** HGV RNA using RT-PCR. Tests of liver functions included serum bilirubin (total and direct), ALT, AST, alkaline phosphatase (ALP), total proteins, and albumin. Written consent was taken from all patients.

Statistical Analysis: IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Data were expressed as Mean ±SD for quantitative parametric measures in addition to both number and percentage for categorized data. Comparison between two independent mean groups for parametric data using Student t-test and comparison between more than 2 patient groups for parametric data using analysis of variance (ANOVA) were carried out. The multiple comparison (Post-hoc test or Least significant difference, LSD) was also followed to investigate the possible statistical significance between each 2 groups. Also, Pearson correlation test was applied to study the possible association between each two variables among each group for parametric data. Chi-square test was applied to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data were studied. $P<0.05$ was considered significant.

RESULTS

This study was carried out on 60 patients between 40- 60 years old, 10% were females and 90% were males in blood donors group and 26.7% were females and 73.3% were males in hemodialysis group.

Liver biochemical profile showed a significant relations with CD4 cells count where CD4 cells count decreased by increasing of ALT (Figure1), AST (Figure2), ALP (Figure 3), total bilirubin (Figure 4) and increased by increasing serum albumin (Figure5). Comparing between CD4 cells count in different groups studied, count in control group was higher than that in the two other groups (Figure 6). Regarding the CD4 cells count and PCR for HGV, patients with HGV have a higher CD4 cells count than patients without HGV (P value = 0.045, Table 1). Also, Table (1) showed higher CD4 cells count in patients with both HIV and HGV than patients with HIV and without HGV (P value < 0.001). Figure (7) showed a comparison between CD4 cells count in HIV cases with and without HGV where, the mean of CD4 cells count in patients with both HIV and HGV is (422.333) which is higher than that in patients with HIV without HGV (117.333).

Results showed that, out of 30 patients of frequent blood donors group, 28 (93.3%) were negative for HIV and 2 (6.7%) were positive for HIV, while in control group 20 (100%) were negative for HIV (Table 2). Also, out of 30 patients of the hemodialysis group, 26 (86.7%) were negative for HIV and 4 (13.3%) were positive for HIV, while in control group 20 (100%) were negative for HIV (Table 2). Figure (8) showed HIV Ab in different groups. Our study showed that, out of 30 patients of frequent blood donors group, 26 (86.7%) were negative for HGV and 4 (13.3%) were positive for HGV, while in control group 20 (100%) were negative for HGV (Table 3). Furthermore, out of 30 patients of

hemodialysis group, 26 (86.7%) were negative for HGV and 4 (13.3%) were positive for HGV, while in control group 20 (100%) were negative for HGV (Table 3). Finally, figure (9) showed that the prevalence of HGV in HD and BD groups was 13.3% while in control group 100% were negative for HGV.

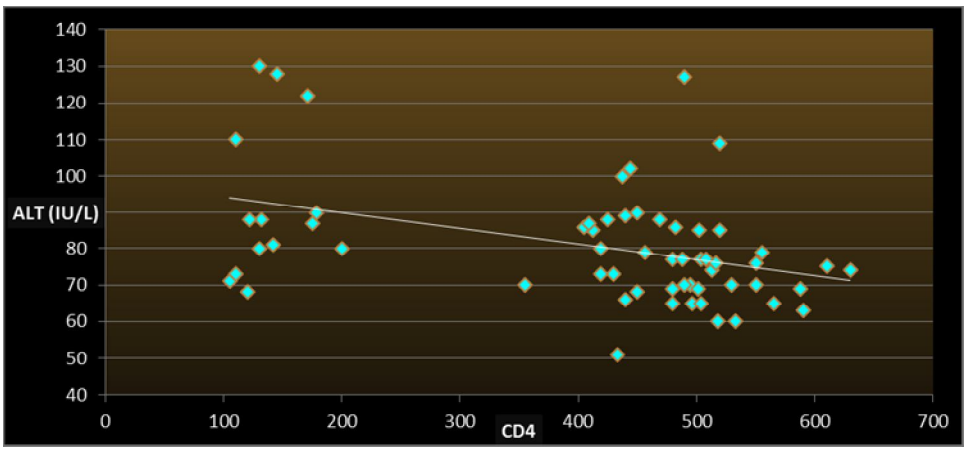

Figure (1): Relation between CD4 cells count and ALT (SGPT).

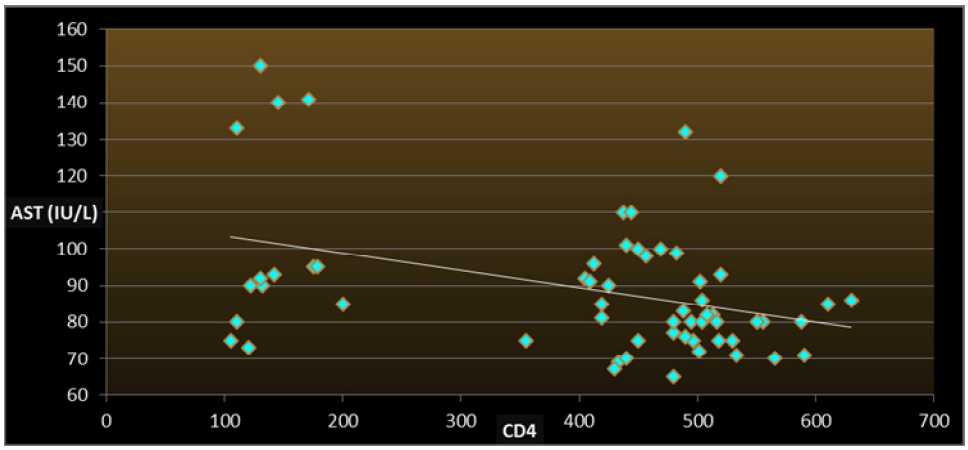

Figure (2): Relation between CD4 cells count and AST (SGOT).

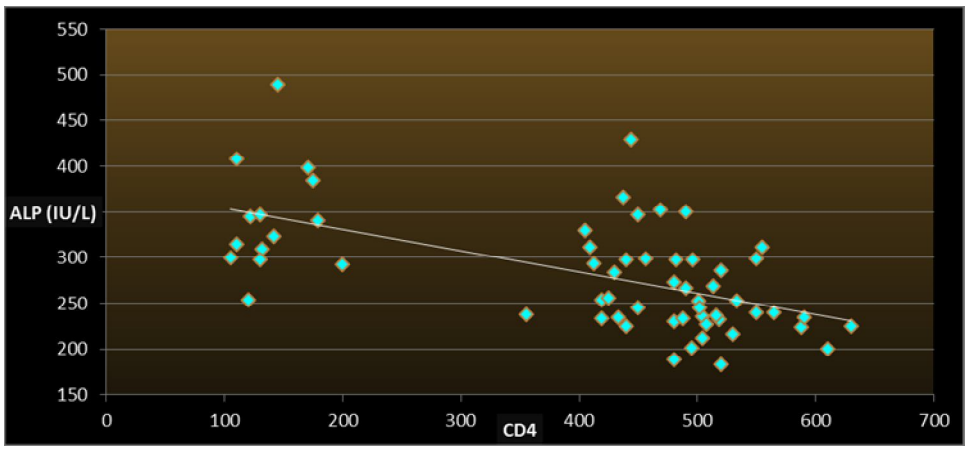

Figure (3): Relation between CD4 cells count and ALP

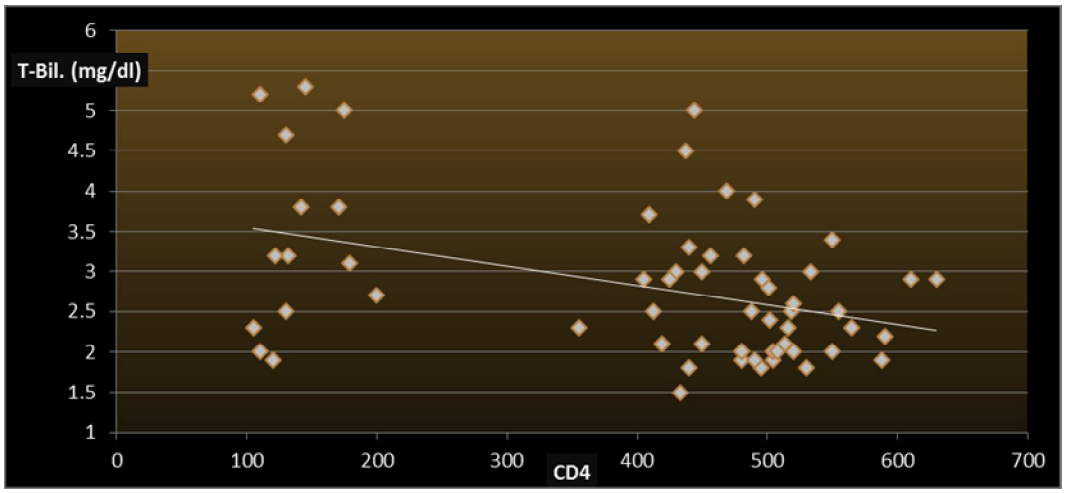

Figure (4): Relation between CD4 cells count and serum bilirubin.

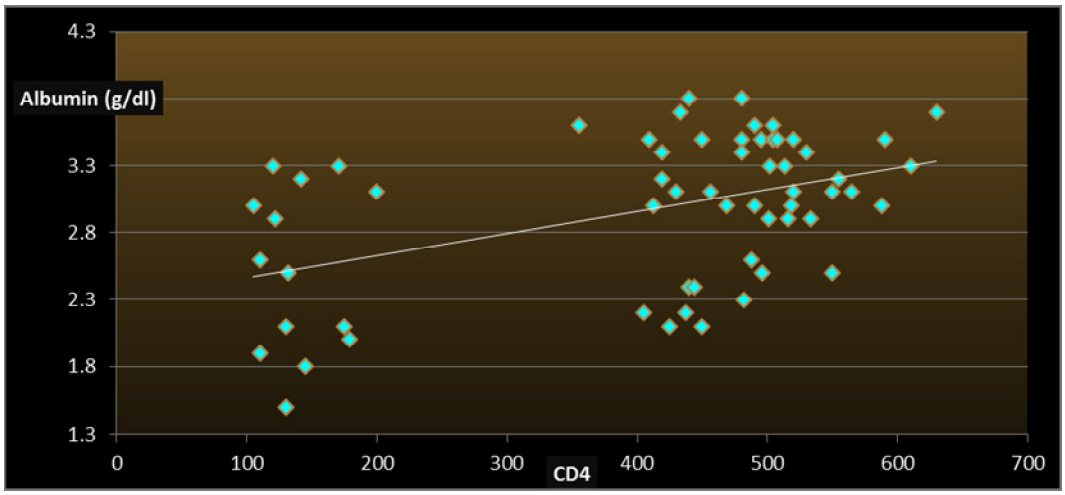

Figure (5) : Relation between CD4 cells count and serum albumin.

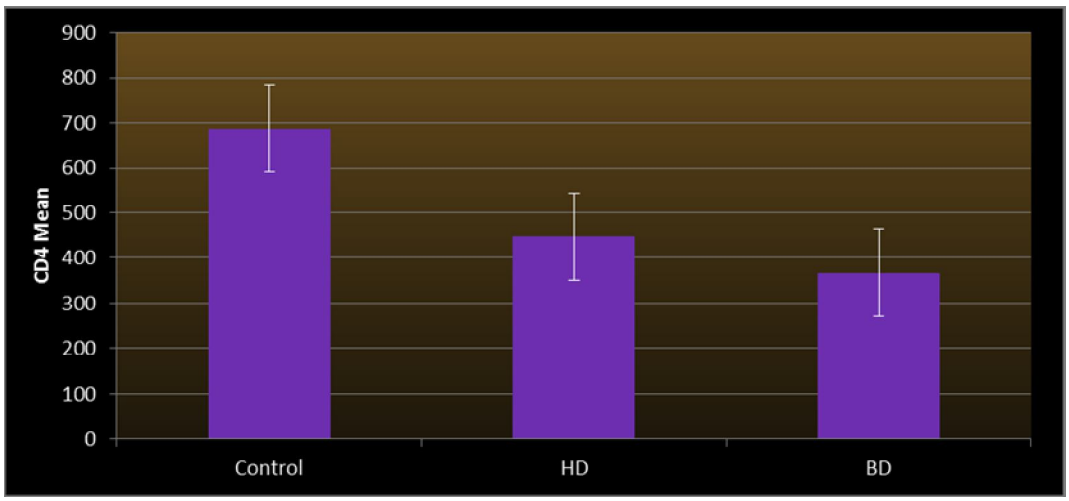

Figure (6): Comparison between CD4 cells count in different studied groups.
HD = Hemodialysis group. BD = Blood donors group.

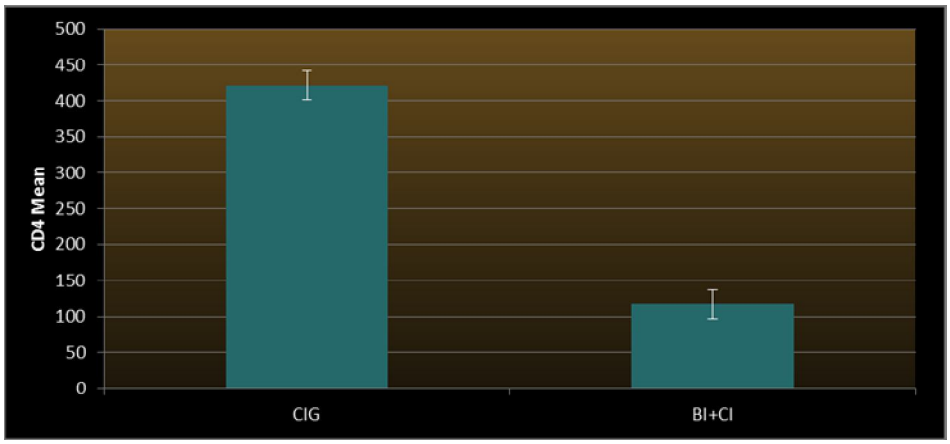

Figure (7): Comparison between CD4 cells count in HIV cases with and without HGV. CIG = HCV+ HIV+ HGV (HIV with HGV), BI+CI = HBV+ HIV and HCV + HIV (HIV without HGV).

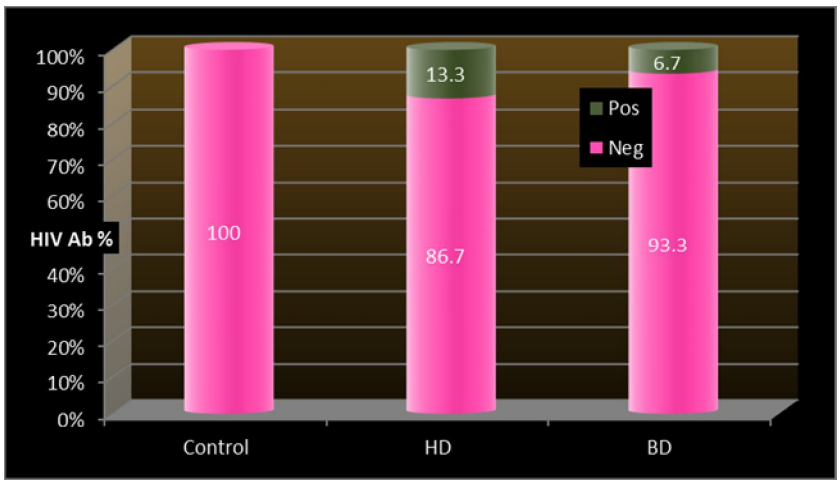

Figure (8): HIV Ab in different groups.
Pos = Positive. Neg =Negative.
HD = Hemodialysis group. BD = Blood donors group.

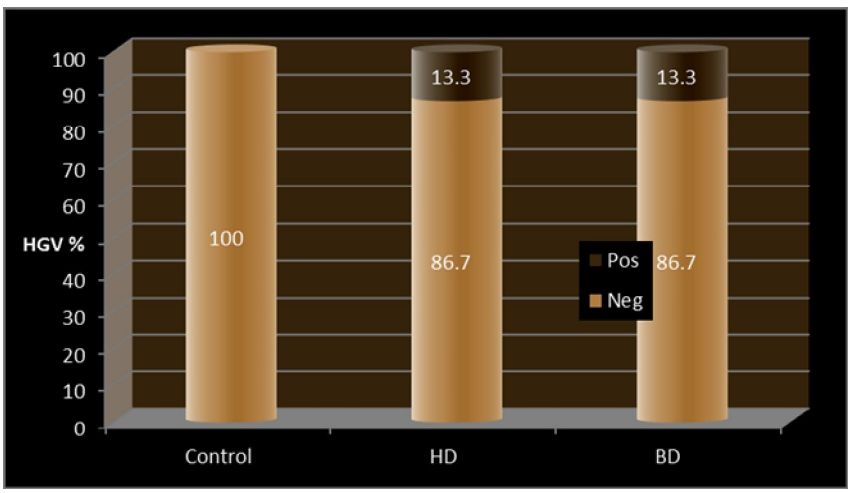

Figure (9): HGV in different groups.
Pos = Positive. Neg =Negative.
HD = Hemodialysis group. BD = Blood donors group.

Table (1): Comparison between CD4 cells count in cases with and without HGV**.**

Parameters / Cases	HGV	n	Mean of CD4	SD	p
CD4	Negative	52	395.25	161.825	0.045
	Positive	8	487.37	99.61	
	HIV without HGV	3	117.333	12.7017	0.001
	HIV with HGV	3	422.333	63.8462	

Table (2): Classification of the blood donors and hemodialysis groups according to detection of HIV

HIVAb / Groups		BD	Control	HD	Total
Negative	Count	28	20	26	74
	%	93.3%	100.0%	86.7%	92.5%
Positive	Count	2	0	4	6
	%	6.7%	0.0%	13.3%	7.5%
Total	Count	30	20	30	80
	%	100.0%	100.0%	100.0%	100.0%

Table (3): Classification of the blood donors and hemodialysis groups according to detection of HGV.

HGV / Groups		BD	Control	HD	Total
Negative	Count	26	20	26	72
	%	86.7%	100.0%	86.7%	90.0%
Positive	Count	4	0	4	8
	%	13.3%	0.0%	13.3%	10.0%
Total	Count	30	20	30	80
	%	100.0%	100.0%	100.0%	100.0%

DISCUSSION

GBV-C infection has been found worldwide and currently infects approximately one sixth of the world's population. About 10–25% of hepatitis C infected patients and 14–36% of drug users who are seropositive for HIV-1 show the evidence of GBV-C infection. It has been classified into six genotypes and many subtypes with distinct geographical distributions **(Feng *et al.*, 2011).** Genotype 1 is predominant in Africa and is divided into five subtypes. Genotype 2 has three subtypes and is found in Europe and America. Genotype 3 is the most common in Asia including Japan and China. Genotype 4 is predominant in Southeast Asia and genotype 5 is only seen in South Africa. Genotype 6 has been described in Indonesia.Genotype 5 appears to be basal in the phylogenetic tree suggesting an African origin for this virus **(Muerhoff *et al.*, 2005).**

Although viremia may persist for years in infected humans, most individuals clear GBV-C RNA and thereafter have detectable antibody to the GBV-C surface envelop glycoprotein E2 **(Stapleton *et al.*, 2004).** The earlier data, and studies demonstrated that GBV-C inhibits HIV replication in vitro suggested that GBV-C replication may be interfering with HIV replication and thus may lead to an improved response to ART **(Xiang *et al.*, 2004)**.

In the present study, liver biochemical profile showed a significant relations with CD4 cells count where CD4 cells count decreased by increasing of ALT, AST, ALP, total bilirubin and decreasing serum albumin. HIV infects vital cells in the human immune system such as T helper cells (specifically CD4+ T cells), macrophages, and dendritic cells **(Cunningham *et al.*, 2010).** HIV infection leads to low levels of CD4+ T cells through a number of mechanisms, including pyroptosis of infected T cells **(Doitsh *et al.*, 2014),** apoptosis of uninfected cells **(Garg *et al.*, 2012),** direct viral killing of infected cells, and killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells **(Kumar and Vinay 2012).** Envelope glycoprotein GP120 (or gp120) is a glycoprotein exposed on the surface of the HIV envelope. Gp 120 plays a vital role in the ability of HIV-1 to enter $CD4^+$ cells **(Wyatt et *al.*, 1998).**

Gendrault *et al.* (1991) and Schmitt *et al.* (1990) reported that HIV may alter liver function by either direct or indirect mechanisms. HIV predominantly infects CD4+ T-cells, monocyte/macrophages and dendritic cells. HIV can directly infect hepatocytes, hepatic stellate cells (HSCs) and Kupffer cells (KCs), where gp120 binding to CXCR4 may induce hepatocyte apoptosis and activation of HSCs, both contributing to fibrosis. HIV infection of the gastrointestinal tract leads to an increase in lipopolysaccharide (LPS) which can stimulate hepatocytes, KCs and HSCs to produce pro- inflammatory cytokines and chemokines which attract activated lymphocytes and monocytes to the liver which may further drive fibrosis.

Concerning CD4 cells count, its count in control group was higher than that found in the two other groups. **Mata-Marín *et al.* (2009)** revealed that, in HIV positive patients, the increase in hepatic enzymes could be secondary to multiple factors such as alcoholism, lipid lowering

drugs, antibiotics, co-infection with hepatotropic viruses, opportunistic organisms as well as direct hepatic damage caused by HIV. Furthermore, some HBV factors on HIV transcription favor enhanced HIV replication leading to faster CD4 T-cell decline in HIV/HBV co-infected individuals **(G?mez-Gonzalo *et al.*, 2001).** In this work, CD4 cells count in patients with HGV was higher than CD4 cells count in patients without HGV. This agreed with results reported by **Stapleton (2003)** who reported that GBV-C (HGV) viremia is also associated with improved markers of HIV disease including higher CD4 T cell counts, lower HIV viral load, and delayed progression to AIDS in many studies. Among the results of present study, patients with both HIV and HGV have a higher CD4 cells count than patients with HIV without HGV. These results were in accordance with that reported by **Cainelli *et al.* (2001)** who reported that active infection with HGV is protective in HIV, and is associated with a reduced risk of death. **Xiang *et al.* (2001)** reported that patients with HGV have a lower mortality rates, higher baseline CD4 T cell counts, and also a slower rate of decline in the number of CD4 T cell. A further evidence of the protective effect of HIV/HGV co-infection is reported by **Williams *et al.* (2004)** who recorded that the course of HIV-1 disease was adversely affected by the clearance of HGV viremia. Suppressing HIV replication with antiretroviral therapy (ART) increases peripheral blood $CD4^+$ T-cell so CD4 cells counts can measure the immune status and ART effectiveness **(Melanie *et al.*, 2012).** CD4 counts should rise 50 to 100 cells per ml in the first year of therapy **(Mandell *et al.*, 2009).** Increasing CD4 cells count leads to slower disease progression, longer survival after AIDS development, and lower HIV serum viral loads **(Shankar *et al.*, 2008).**

Nattermann *et al.* (2003) stated that GBV-C E2 protein can bind to CD81 on T cells. This in turn results in the release of RANTES (regulated-upon-activation, normal T cell expressed and secreted), which binds to and blocks the chemokine receptor CCR5. As CCR5 mediates HIV viral entry into T cells, through this process, GBV-C could act to inhibit HIV viral replication. Both GBV-C infection and expression of two GBV-C proteins inhibit HIV replication in human CD4+ T cells **(Bhattarai and Stapleton 2012).** GBV-C infection modestly alters T cell homeostasis in vivo through various mechanisms, including modulation of chemokine and cytokine release and receptor expression, and by diminution of T cell activation, proliferation and apoptosis, all of which may contribute to improved HIV clinical outcomes (**Stapleton *et al.*, 2003).**

Out of 30 patients of blood donors group, 13.3% were positive for HGV, while in control group 100% were negative. In different studies around the world, a higher and a lower rates of HGV in blood donors are reported. Concerning hemodialysis group, 13.3% were positive for HIV, while in control group 100% were negative for HIV which was a higher prevalence than that reported by **Tokars *et al.* (2002)** who concluded that, in the year 2000 in USA, 1.5% of dialysis patients were reported to have HIV infection. . During the years 1995–1999, the incidence of HIV in end stage renal dialysis (ESRD) for African- American

men was ranging from 6.5 % - 8.5% **(Eggers and Kimmel 2004),** which is also a lower prevalence than that in present study.

Out of 30 patients of hemodialysis group, 13.3% were positive for HGV while in control group 100% were negative for HGV. In studies around the world, a higher and a lower rates of HGV in hemodialysis group are reported. A higher prevalence is found in a study in patients undergoing kidney transplantation in Italy, it is 24% **(De Filippi *et al.*, 2001),** while it is 50% among the patients undergoing hemodialysis in Germany **(Heringlake *et al.*, 1996),** and 24.3% among those undergoing hemodialysis in South Africa **(Sathar *et al.*, 1999).** A prevalence of 12.8% in Brazil **(Watanabe *et al.*, 2003)** and 4.5% in Japan **(Okuda *et al.*, 2000)** are reported which is considered a lower prevalence.

CONCLUSION

HGV infection has a moderate frequency among hepatic hemodialysis, and frequent blood donors. HIV co-infection with HGV was associated with significantly high CD4 cell count suggesting a beneficial effect of HGV infection on HIV co-infected patients.

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خلفية البحث : يصنف الفيروس الكبدى (جى) من الفيروسات ذات الحمض النووى الريبوزى. ونظرا لوجود طرق مشتركة لانتقال فيروس نقص المناعة وفيروسات الكبد (بى) و(سى) فإنه من المحتمل وجود عدوى متزامنة بفيروس (جى) بين المصابين بفيروس (بى) أو (سى) أو كلاهما معا.

الهدف من البحث: تعيين نسبة الإصابة بفيروس (جى) مع أو بدون فيروس نقص المناعة البشرية، وتأثير لفيروس (جى) على مسار فيروس نقص المناعة البشرية فى مرضى التهاب الكبد المزمن المتبرعين بالدم بصفة متكررة سابقا ، ومرضى الغسيل الكلوى.

مواد وطرق البحث: تم تعيين 60 مريضا تتراوح أعمارهم بين 40- 60 سنة ، 10 ٪ من الإناث، 90 ٪ من الذكور في مجموعة المتبرعين بالدم، و أيضا 26.7 ٪ من الإناث و 73.3 من الذكور في مجموعة غسيل الكلى، وجميع الأشخاص يعانون من مرض الكبد المزمن لتعيين نسبة الإصابة بفيروس (جى) بينهم مع أو بدون فيروس نقص المناعة البشرية، وتأثير لفيروس (جى) على مسار فيروس نقص المناعة البشرية بالإضافة إلى 20 شخصا لم يتعرضوا لالتهاب الكبد كمجموعة تحكم. وقد تم إخضاع جميع أفراد الدراسة لإكمال التاريخ المرضي والفحص السريري وكذلك الفحوص المختبرية لتقدير عدد خلايا CD4 ، تعيين فيروس (بى) و (سى) و فيروس نقص المناعة البشرية بواسطة الإليزا، كما تم تعيين الفيروس (جى) بواسطة PCR . وشملت إختبارات وظائف الكبد البيليروبين في الدم، و إنزيمات الكبد (ALT, AST, ALP) ، ومجموع البروتينات، و الزلال.

النتائج: أظهرت التحاليل الكيميائية الحيوية علاقات معبرة مع عدد خلايا CD4 حيث أن عدد خلايا CD4 إنخفض بإرتفاع نسب كل من ALT وAST والفوسفاتيز القلوي (ALP)، والبيليروبين الكلي الذى إرتفع بإرتفاع زلال المصل. وقد وجد أن عدد خلايا CD4 أعلى فى المرضى

المصابين بالفيروس الكبدى (جى) عنه فى المرضى الغير مصابين به. كما لوحظ أن مرضى فيروس نقص المناعة البشرية الذين لديهم إصابة متزامنة بالفيروس الكبدى (جى) لديهم عدد من خلايا CD4 أعلى من أولئك الغير مصابين إصابة متزامنة بالفيروس الكبدى (جى). وأشارت النتائج إلى أن، من أصل 30 مريضا من المتبرعين بالدم، 28 (93.3٪) أعطوا نتائجًا سلبية لفيروس نقص المناعة البشرية، وأعطى 2 (6.7%) نتائجًا إيجابية لفيروس نقص المناعة البشرية. وفيما يتعلق بمجموعة غسيل الكلى ، من أصل 30 مريضا أعطى 26 (86.7٪) نتائجًا سلبية لفيروس نقص المناعة البشرية، وأعطى 4 (13.3%) نتائجًا إيجابية لفيروس نقص المناعة البشرية. و في حالة مجموعة المتبرعين بالدم، من أصل 30 مريضا، أعطى 26 (86.7٪) نتائجًا سلبية للفيروس الكبدى (جى) و أعطى 4 (13.3%) نتائج إيجابية وفى مجموعة غسيل الكلى ، من أصل 30 مريضا أعطى 26 (86.7٪) نتائجًا سلبية للفيروس الكبدى (جى) وأعطى 4 (13.3%) نتائجًا إيجابية.

وقد لوحظ إرتباط الفيروس الكبدى (جى) بإرتفاع فى عدد خلايا CD4 إرتفاعًا معبرًا مما يدل على تأثير مفيد للفيروس الكبدى (جى) فى مرضى فيروس نقص المناعة البشرية.

الخلاصة: يوجد الفيروس الكبدى (جى) بنسبة معتدلة بين مرضى إلتهاب الكبد المزمن و إرتباط الفيروس الكبدى (جى) بإرتفاع فى عدد خلايا CD4 إرتفاعًا معبرا يدل على تأثير مفيد للفيروس الكبدى (جى) فى العدوى المتزامنة بفيروس نقص المناعة البشرية.