# SEN VIRUS INFECTION AND ITS RELATION TO LIVER DISEASE

Thesis

*Submitted for partial fulfillment of the Master degree in Clinical and Chemical Pathology*

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# List of Abbreviations

| | |
|---|---|
| 5\ UTR | 5\ untranslating region |
| 5\NCR | 5\ non coding region |
| Bp | Base pair |
| CBC | Complete blood count |
| cDNA | Cyclic DNA |
| CMV | Cytomegaloviurs |
| dATP | Deoxy adenosine triphosphate |
| dCTP | Deoxy cytosine triphosphate |
| dGTP | Deoxy guanosine triphosphate |
| DMSO | Dimethyle sulfoxide |
| dNTPs | Deoxy nucleotide triphosphates |
| dTTP | Deoxy thymidine triphosphate |
| EIA | Enzyme linked immunoassay |
| FA | fluorescence anti-body |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HGV | Hepatitis G virus |
| HIV | Human immune deficiency virus |
| HRP | Horseradish peroxidase |
| IDU | Intravenous drug user |
| IFN | Interferon |
| Mu | Million unitrs |
| n.m | Nanometer |

| | |
|---|---|
| n.t | Nucleotide |
| ORFs | Open reading frames |
| PCR | Polymerase chain reaction |
| PORFs | Putative open reading frames |
| PT | Prothrombin time |
| RT-PCR | Reverse transcription polymerase chain reaction |
| S.S | single stranded |
| SENV | SEN virus |
| SENV-A | SEN virus type A |
| TLMV | TT virus like mini virus |
| TTV | TT virus |
| UV | Ultra violet |
| UV | Ultra violet |

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First and foremost thanks to **ALLAH** whose magnificent help was factor in accomplishing this work.

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# INTRODUCTION AND AIM OF THE WORK

Five hepatitis viruses (A-E) cause more than 80% of cases of viral hepatitis. However, the fact that nearly 20% of individuals with acute hepatitis test negative for all known hepatitis viruses, as do up to 10% of patients with transfusion associated hepatitis suggests the existence of other viral hepatitis agents ***(Alter et al., 1999; Shibata et al., 2001 and Moriyama et al., 2005).***

Investigators have continued to search for other infectious agents responsible for non A-E hepatitis. Two novel isolates were identified from patients with non-A non-B hepatitis and were designated hepatitis G virus (HGV) and TT virus (TTV) respectively ***(Simons et al., 1995 and Nishizawa et al., 1997).*** Although both (HGV) and TTV spread universally most recent studies indicate that both (HGV) and (TTV) do not cause liver disease, unlike classic hepatitis viruses ***(Zhu et al., 2003 and DAI et al., 2004).***

In 1999 in Italy a new virus was isolated from the serum of HIV positive patient initials (SEN) who used intravenous drugs and had post -transfusion hepatitis of unknown aetiology. Eight different strains of SENV, named SENV-A to SENV-H were identified and provisionally classified as members of the Circoviridae family ***(Tanaka et al., 2001).*** Only SENV-D and SENV-H Seem to cause post transfusion hepatitis ***(Umemura et***

***al., 2001 and Huang et al., 2005)*** The pathway of transmission of SENV infection is not known so, far but the infection by this virus is frequent in recipients of blood transfusion and liver grafts and in I.V drug addicts. This suggests possible parentral transmission of infection. Other routes of transmission of the infection are also possible as the virus can be detected in a significant proportion of young subjects without the risk of parentral infection in the case history ***(Abdurrahman et al., 2005).***

Eight different SENV isolates (A-H) have been described. These viruses have varying prevalences in different populations. SENV-D and SENV-H are more prevalent in serum samples from patients with transfusion associated non A-E hepatitis and are found-less frequently in serum samples from healthy blood donors ***(DAI et al., 2004).***

The role of SENV-D and SENV-H in the causation of transfusion associated non A-E hepatitis has been evaluated ***(Umemura et al., 2001)*** Also, the association of SENV infection with liver cell damage is far from clear, and further studies are needed to investigate the clinical relevance of SENV infection world wide ***(Pirovano et al., 2005).***

The SENV variants are assayed by polymerase chain reaction (PCR) to investigate its role in the causation of transfusion associated non A-E hepatitis ***(Abdurrahman et al., 2005).***

## Aim of the Work

The aim of our work is to identify the prevalence of SEN-V infection and to clarify a relationship between SEN-V infection and liver disease.

# INTRODUCTION

Five hepatitis viruses (A–E) cause more than 80% of cases of viral hepatitis. However, the fact that nearly 20% of individuals with acute hepatitis test negative for all known hepatitis viruses, as do up to 10% of patients with transfusion associated hepatitis suggests the existence of other viral hepatitis agents ***(Alter et al., 1999; Shibata et al., 2001 and Moriyama et al., 2005)***.

Investigators have continued to search for other infectious agents responsible for non A-E hepatitis. Two novel isolates were identified from patients with non-A non-B hepatitis and were designated hepatitis G virus (HGV) and TT virus (TTV) respectively ***(Simons et al., 1995)*** and ***(Nishizawa et al., 1997)***. Although both (HGV) and (TTV) spread universally, most recent studies indicate that both (HGV) and (TTV) do not cause liver disease, unlike classic hepatitis viruses ***(Zhu et al., 2003 and DAI et al., 2004)***.

In 1999 in **Italy** a new virus was isolated from the serum of HIV positive patient initials (SEN) who used intravenous drugs and had post – transfusion hepatitis of unknown aetiology. Eight different strains of SENV, named SENV-A to SENV-H were identified and provisionally classified as members of the Circoviridae family ***(Tanaka et al., 2004)***. Only SENV-D and SENV-H Seem to cause post transfusion hepatitis

***(Umemura et al., 2003 and Huang et al., 2005)***. The pathway of transmission of SENV infection is not known so far, but the infection by this virus is frequent in recipients of blood transfusion and liver grafts and in I.V drug addicts. This suggests possible parentral transmission of infection. Other routes of transmission of the infection are also possible as the virus can be detected in a significant proportion of young subjects without the risk of parentral infection in the case history ***(Sagir et al., 2005)***.

The eight different SENV isolates (A-H) have been described, have varying prevalences in different populations. SENV-D and SENV-H are more prevalent in serum samples from patients with transfusion associated non A-E hepatitis and are found less frequently in serum samples from healthy blood donors ***(DAI et al., 2004)***.

The role of SENV-D and SENV-H in the causation of transfusion associated non A-E hepatitis has been evaluated ***(Umemura et al., 2003)***. Also, the association of SENV infection with liver cell damage is far from clear, and further studies are needed to investigate the clinical relevance of SENV infection world wide ***(Pirovano et al., 2005)***.

The SENV variants are assayed by polymerase chain reaction (PCR) to investigate its role in the causation of transfusion associated non A-E hepatitis ***(Sagir et al., 2005)***.

# HISTORICAL ASPECT

After the discovery of hepatitis C virus ***(Choo et al., 1989)***. 10-20% of persons with acute hepatitis, 24-47% of those with fulminant hepatitis and 5% of those with chronic hepatitis remained negative for all known hepatitis viruses and were classified as having non A-E hepatitis ***(Alter et al., 1999)***.

Investigators have continued to search for other infectious agents responsible for non A, non B hepatitis. As candidates for unknown hepatitis viruses, 2 novel isolates were identified from patients with non A, non B hepatitis and were designated hepatitis G virus (HGV) and TT virus (TTV) respectively ***(Nishizawa et al., 1997)***.

Although HGV and TTV have been claimed to be prevalent in chronic liver diseases patients, most studies have indicated that neither virus causes liver disease ***(Zhu et al., 2003 and DAI et al., 2004)***.

In 1999 in **Italy** a previously unidentified virus was detected in the blood of a human immunodeficiency virus (HIV) infected drug user (IDU) and named SEN virus (SENV) after the initials of the infected patient ***(Primi et al., 2000)***.

**Classification and Morphology**

The SENV belongs to the superfamily of TTV- related viruses ***(Hino et al., 2002)*** phylogenetic analysis of SENV showed the existence of eight different genotypes, named SENV A-H, each genotype differs from one another by a divergence in the nucleotide sequence of at least 25% ***(Sagir et al., 2005)***.

Although structurally similar to TTV, SENV has less than 55% sequence homology and less than 37% amino acid homology with the TTV prototype ***(Huang et al., 2005)*** (fig:1).

The SENV is grouped within the TTV- Related family of viruses Circoviridae. This family additionally includes: TTV, TTV-like minivirus (TLMV), SANBAN, Tuso1, PMV and YONBAN. Within the circoviridae family, SENV is clustered with SANBAN and Tuso1, a group that is the most recent of the family, which has evolved from a common ancestor ***(Sagir et al., 2005)***. The SENV has a size of 26 nanometer (n.m) and a genome length of ~ 3600-3800 nucleotide (nt) the ability of SENV to persist may be related to its hypervariable regions with mutation rates of 7.32 X $10^{-4}$ per site per year ***(Umemura et al., 2003 and Spataro et al., 2006)***.