Project on

A Review article on viral hepatitis, pathogenesis, Diagnosis and Treatment

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

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APPROVAL

This project paper, A Review in the field of antiviral treatments for dengue virus infections, submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, A Review in the field of Diagnosis, Pathology and

Treatment of hepatitis , is done by me under the supervision Ms. Tahmina Afroz Assistant Professor, I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree .

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I might want to communicate my profound applause to the All-powerful Allah who has given me the capacity to finish my undertaking work and the chance to concentrate in this subject. I'm a lot of thankful to my honorable project supervisor Ms. Tahmina Afroz Assistant Professor, Department of Pharmacy, Daffodil International University.

I would like to express my humble regards to Dr. Muniruddin Ahmed, Professor and Head, Department of Pharmacy, Daffodil International University. I also wish to offer my respect to all of the teachers of Pharmacy Department, Daffodil International University and thankful to other members for their excellent cooperation with us.

Finally, I would like to express my gratitude towards my parents and other family members for their kind cooperation and encouragement which helped me in completion of this project.

My Parents

The persons who always encourage me in every sphere of my life

Abstract

Hepatitis is a liver infectious disease. Liver infection mainly cause by hepatitis A, B, C, D and E virous[1]. Other cause also presents, like alcohol, some medicine and others. Hepatitis A & E mainly cause acute infection and they are self-limiting disease but hepatitis B, C, D are most dangerous virous[1][2]. These virous can create chronic infection and make liver cirrhosis & cancer. Hepatitis D infection occurs when hepatitis B infection already present previously[1][3]. Hepatitis D infection are two type one is coinfection and other is super infection. Hepatitis A and normally cause acute infection[2][11].Hepatitis E virous and hepatitis C virous do not have vaccine but others hepatitis A, B, D have vaccine[12]. If we treat hepatitis B, hepatitis D will treat automatic. Because hepatitis D infection is a co-infection[30]. There are many medicine discovered to treat hepatitis B and C[22]. like Reverse Transcriptase inhibitors (for hepatitis B) like lamivudine, entecauin, Tenofovir disoproxil fumara, emtricitabine, tenofovir alafenamide (NRTI'S) and adefovir, tenofovir (NTRIT'S) and also IFN-ALFA[44][55]. And For hepatitis C virous discovered many drug like 1. protease inhibitors(simeprevir, paritaprevir) 2. NS5A inhibitors (ledipasvir, velpatasvir) 3.NS5D inhibitors (sofosbuvir, dasabuvir) 4. Ribavirin[78]. Worldwide in 2015, hepatitis A occurred in about 114 million people, chronic hepatitis B affected about 343 million people and chronic hepatitis C about 142 million people[81][66]. In the United States, NASH affects about 11 million people and alcoholic hepatitis affects about 5 million people[33]. Hepatitis results in more than a million deaths a year, most of which occur indirectly from liver scarring or liver cancer. In the United States, hepatitis A is estimated to occur in about 2,500 people a year and results in about 75 deaths. The word is derived from the Greek hêpar meaning liver and -itis meaning inflammation[61].

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Chapter one

Introduction

Introduction : Hepatitis is inflammation of the liver towel[1]. Some people or creatures with hepatitis have no symptoms, whereas others develop unheroic abrasion of the skin and whites of the eyes(hostility), poor appetite, puking, frazzle, abdominal pain, and diarrhea[1][2]. Hepatitis is acute if it resolves within six months, and habitual if it lasts longer than six months[2]. Acute hepatitis can resolve on its own, progress to habitual hepatitis, or(infrequently) affect in acute liver failure[3]. habitual hepatitis may progress to scarring of the liver(cirrhosis), liver failure, and liver cancer[4][5].

Hepatitis is most generally caused by the contagion hepatovirus A, B, C, D, and E[1][2][5]. Other contagions can also beget liver inflammation, including cytomegalovirus, Epstein – Barr contagion, and unheroic fever contagion[4]. Other common causes of hepatitis include heavy alcohol use, certain specifics, poisons, other infections, autoimmune conditions, andnon-alcoholic steatohepatitis(NASH[)][6]. Hepatitis A and E are substantially spread by defiled food and water. Hepatitis B is substantially sexually transmitted, but may also be passed from mama to baby during gestation or parturition and spread through infected blood[7]. Hepatitis C is generally spread through infected blood similar as may do during needle sharing by intravenous medicine druggies[8]. Hepatitis D can only infect people formerly infected with hepatitis[10]. Hepatitis A, B, and D are preventable with immunization. specifics may be used to treat habitual viral hepatitis[11]. Antiviral specifics are recommended in all with habitual hepatitis C, except those with conditions that limit their life expectation[12]. There's no specific treatment for NASH, physical exertion, a healthy diet, and weight loss are recommended. Autoimmune hepatitis may be treated with specifics to suppress the vulnerable system. A liver transplant may be an option in both acute and habitual liver failure[12][13].

Worldwide in 2015, hepatitis A passed in about 114 million people[13], habitual hepatitis B affected about 343 million people and habitual hepatitis C about 142 million people.In the United States[15][16],

NASH affects about 11 million people and alcoholic hepatitis affects about 5 million people[15]. Hepatitis results in further than a million deaths a time, ultimate of which do indirectly from liver scarring or liver cancer[16]. In the United States, hepatitis A is estimated to do in about, 500 people a time and results in about 75 deaths[16][17]. The word is derived from the Greek hêpar, meaning liver and itis meaning inflammation. and developed nations, and is anticipated to rise in several developing countries. hepatitis A infections are tone-limited events, they are associated with significant costs in the United States[17].

It has been estimated that direct and indirect costs are roughly$ 1817 and$ 2459 singly per case, and that an Overall, hepatitis accounts for a significant portion of healthcare expenditures in both developing normal of 27 work days is lost per infected grown-up[18]. A 1997 report demonstrated that a single hospitalization related to hepatitis A bring an normal of$, 900 and reacted in around$ 500 million in total periodic healthcare costs[19]. Cost effectiveness studies have set up wide vaccination of grown- ups to not be realizable, but have stated that a combination hepatitis A and B vaccination of children and at trouble groups(people from endemic areas, healthcare workers) may be[19][20].

Hepatitis B accounts for a much larger chance of health care spending in endemic regions like Asia[18]. In 1997 it reckoned for 3.2 of South Korea's total health care expenditures and reacted in$ 696 million in directcosts[16]. A large maturity of that sum was spent on treating complaint symptoms and complications. habitual hepatitis B infections are not as endemic in the United States, but reckoned for $ 357 million in hospitalization costs in the time 1990. That number grew to$1.5 billion in 2003, but remained stable as of 2006, which may be attributable to the prolusion of effective drug antidotes and vaccination campaigns[8]. People infected with habitual hepatitis C tend to be frequent druggies of the health care system encyclopedically[14].

It has been estimated that a person infected with hepatitis C in the United States will affect in a yearly cost of $ 691[16].That number nearly doubles to$,227 for people with compensated (stable) cirrhosis, while the yearly cost of people with decompensated(worsening) cirrhosis is nearly five times as large at$,682. The wide- ranging goods of hepatitis make it delicate to estimate circular costs, but studies have suspected that the total cost is$6.5 billion annually in the United States. In Canada, 56 of HCV related costs are attributable to cirrhosis and total expenditures related to the contagion are anticipated to peak at CAD $ 396 million in the time 2032[16][17][20].

Causing factor of hepatitis

Hepatitis is a disease cause by virous. The responsible virous are hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E. hepatitis A virous make hepatitis a disease. Hepatitis B virous make

hepatitis b disease. . Hepatitis C virous make hepatitis c disease. . Hepatitis D virous make hepatitis d disease. . Hepatitis E virous make hepatitis e disease[77][78][80].

virology Hepatitis A virous

Hepatitis a disease cause by hepatitis A virous. Hepatitis A virous cause acute infection. This virous do not cause chronic infection normally[77]. More than 6 month infection called chronic infection[78].

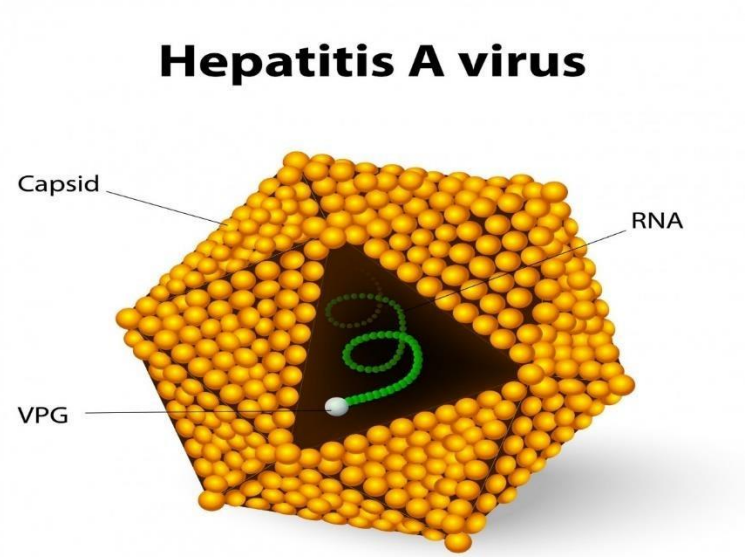

Figure 1 : hepatitis a virous

Hepatitis a virous do not contain envelope. It is a single stranded RNA virous(+SSRNA).+SSRNA means this single stranded RNA virous can make protein by using host ribosome. The outer most layer of this virous is capsid[77]. This capsid layer made by protein. And between the capsid this virous contain many types of enzyme. And in the middle position virous contain +SSRNA. Hepatitis A contagion is an enteric picornavirus. Its genome is a single stranded RNA patch of positive- beachfront opposition of 7478 bases. This sequence canons for a polyprotein which is reused to give rise to viral proteins VP- 1, VP- 2, VP- 3 and others[80].

Hepatitis B virous

Hepatitis b disease cause by hepatitis B virous. Hepatitis B virous cause acute and also chronic infection. This virous are mainly responsible for chronic infection normally. More than 6 month of hepatitis B infection called chronic infection[77].

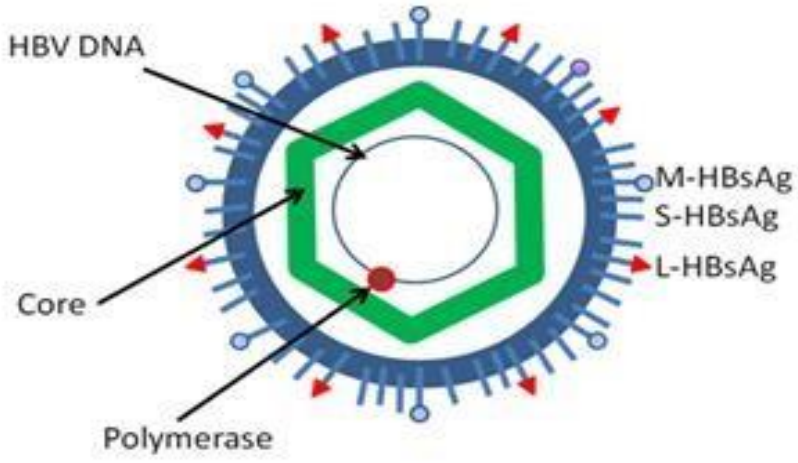

Figure 2: Hepatitis B virous [77]

Hepatitis b virous contain envelope[78]. It is a double stranded DNAvirous(pDNA). pDNA means this double stranded virous can not contain 100% double stand.It contain almost 70% of double stand.The outer most layer of this virous is capsid.This capsid layer made by protein. And between the capsid this virous contain many types of enzyme[77]. And in the middle position virous contain pDNA. The contagious HBV virion(Dane flyspeck) has a globular, double- shelled structure 42 nm in periphery, conforming of a lipid envelope containing HBsAg that surrounds an inner nucleocapsid composed of hepatitis B core antigen(HBcAg) perplexed with virally decoded polymerase and the viral DNA genome[77][82].

Hepatitis C virous

Hepatitis c disease cause by hepatitis C virous. Hepatitis C virous cause acute and also chronic infection. This virous are mainly responsible for chronic infection normally. More than 6 month of hepatitis C infection called chronic infection[77][78][82].

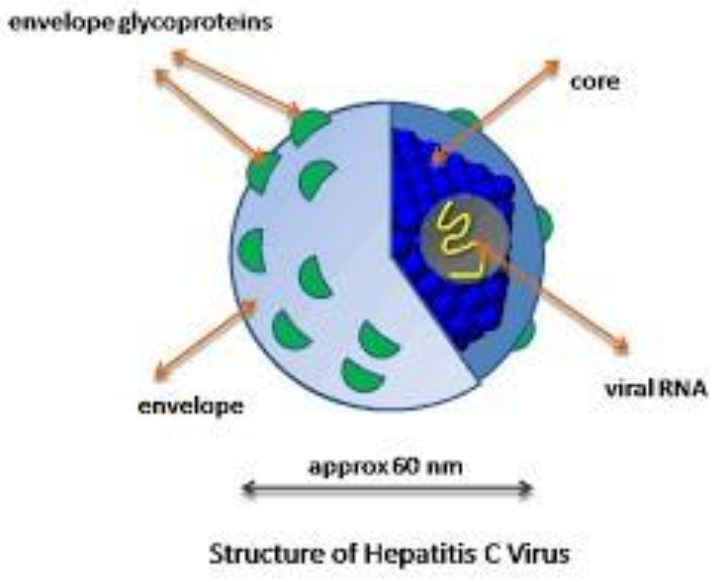

Figure 2: Hepatitis c virous[77]

Hepatitis c virous do not contain envelope[77]. It is a single stranded RNA virous(+SSRNA).+SSRNA means this single stranded RNA virous can make protein by using host ribosome. The outer most layer of this virous is capsid. This capsid layer made by protein. And between the capsid this virous contain many types of enzyme. And in the middle position virous contain +SSRNA[78].

Hepatitis D virous

Mainly it is a chronic infection. Hepatitis D infection occurs when hepatitis b infection already present previously[78][82]. Hepatitis D infection occurs in case, one is coinfection and other is super infection. Same time hepatitis B and Hepatitis D infection call coinfection[64]. And when hepatitis B infection occurs first and hepatitis D infection occurs some days later of b infection. Hepatitis d disease cause by hepatitis D virous. Hepatitis D virous cause chronic infection. This virous are mainly responsible for chronic infection normally[65][77].

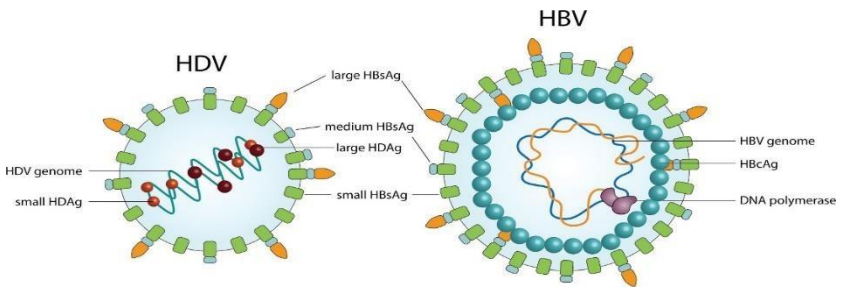

Figure 4 : hepatitis D virous [78]

Hepatitis D virous contain envelope[77]. It is a single stranded RNA virous(-SSRNA).-SSRNA means this single stranded RNA virous cannot make protein by using host ribosome. The outer most layer of this virous is capsid. This capsid layer made by protein. And between the capsid this virous contain many types of enzyme. And in the middle position virous contain -SSRNA. But this RNA is circular[78][82].

Hepatitis E virous

Hepatitis a disease cause by hepatitis E virous. Hepatitis E virous can cause acute and chronic infection. This virous do not cause chronic infection normally. In case of immunocompromise patient can cause chronic infection. More than 6-month infection called chronic infection[77][78].

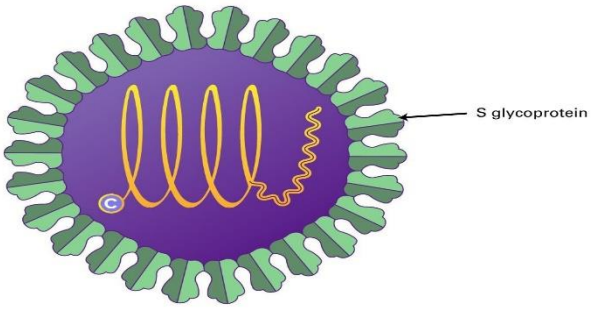

Figure 5: hepatitis E virous[77]

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Transmission :

HAV transmission

hepatitis A virous is mainly transmitted through fecal-oral route. When water or food are disinfected by affected person stool[21]. And that is main cause of hepatitis A virous transmission not through casual contact. People can prevent this virous by personal hygiene and also by unharmful drinking water[22].

HBV Transmission

Hepatitis V virous primarily transmitted in three way[21]. Firstly sexual transmission, secondly blood transmission, and thirdly perinatal transmission. If sex partner are affected by hepatitis B virous that time other partner will also affected by hepatitis B and that is called sexual transmission[25]. If affected person blood transfer to unaffected person that time that person will also affected and that is called blood transmission[23]. When affected pregnant women concept baby that time baby also affected by this dangerous virous and that is called perinatal transmission. Affected needles or syringes can also transmission of hepatitis B[24].

HCV Transmission

Hepatitis V virous primarily transmitted in three way[25]. Firstly sexual transmission, secondly blood transmission, and thirdly perinatal transmission. If sex partner are affected by hepatitis B virous that time other partner will also affected by hepatitis B and that is called sexual transmission. If affected person blood transfer to unaffected person that time that person will also affected and that is called blood transmission[26]. When affected pregnant women concept baby that time baby also affected by this dangerous virous and that is called perinatal transmission. Affected needles of syringes can also transmission of hepatitis B[27].

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Chapter two

Purpose of the study

- To learn about hepatitis disease and causing factor.
- To have a better grasp of the diagnostic procedures used to diagnose this disease.
- To learn about transmission procedure and better treatment procedure.
- To know what percent of people aware about this dangerous disease.
- To know pathogenesis of hepatitis.
- The goals of this project are to get an inclusive considerate of the medical problem being researched.
- To learn more about the variables that contribute to the development of Dengue virus infection.
- To gain a systematic understanding of the disease, as well as its cause, signs and symptoms, consequences, and medical and nursing treatment choices.

Chapter three

Methodology

3.1 Materials and Procedures

The methods employed in this investigation are discussed in this chapter. It is a explanation of the study environment. The study population, the study sample, the research equipment, the technique, and the data analysis are all factors to consider.

3.2 Research Methodology

This is a summary of prior studies on different clinical trials as a dengue virus disease treatment.

3.3 Inclusion and Exclusion Criteria

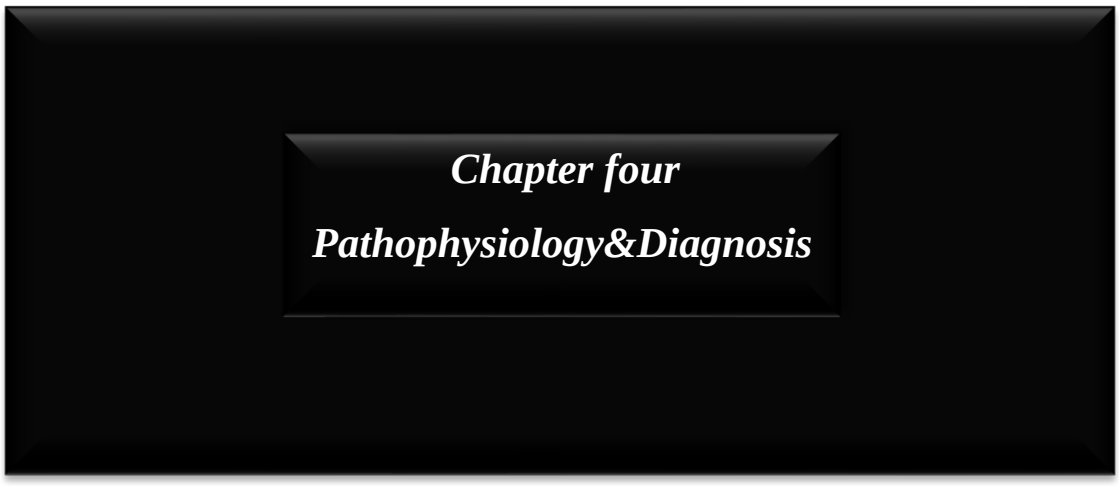
All studies on Drug candidates in clinical trials for dengue virus disease.

3.4 Data Collection Procedure

Data was gathered directly from prior study articles, while another portion was gathered through searching the internet for relevant information. The activities of many treatments were recorded.

3.5 Method of data analysis

All of the information gathered from prior study publications was numerically coded and imported.



Pathology Of Virous: In case of SSRNA VIROUS it will be positive or negative inter into liver cell by endocytosis. We know the SSRNA virous are HAV, HBV, HCV, HDV, HEV .[29][30] After inter into cell these virous disappear all shape and only present SSRNA. At first disappear outer envelope then capsid[31]. All viral component come out with SSRNA. This SSRNA goes to host liver cell ribosome and produce different type of protein like capsomeres(it is important for

capsid), some type of antigen(for put of surface), RNA polymerases, some types of DN A polymerases and so other many enzyme[32].

And all these component goes to Golgi or endoplasmic reticulum for further modification. Golgi apparatus packed all component in many types' vesicles. These packed proteins will be use later for next generation virous. Like RNA dependent RNA polymerases make more and more viral SSRNA (daughter) by using mother SSRNA templet[30][32].

These newly make SSRNA, RNA polymerases, surface antigen, varies type of enzyme make more and more daughter SSRNA virous. And these new virous come out of liver cell by rupture the host liver cell and damage the cell, attack another new liver host cell[31][33].

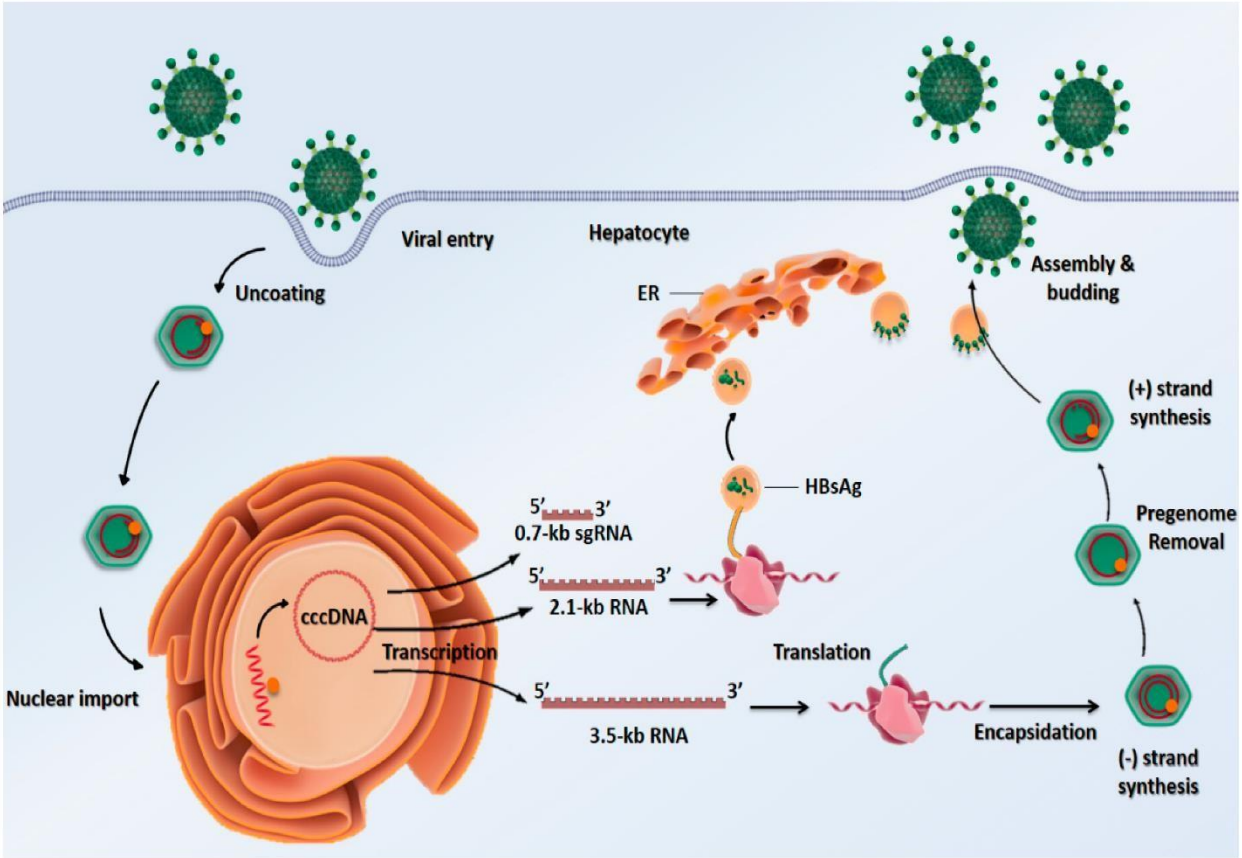


Figure 6 : ss RNA virous infect cell [32]

In case of pDNA virous, in same way inter into host liver cell and disappear all structure accept pDNA . After that this pDNA inter into nucleus that time DNA repair enzyme come and repair the hole double stranded DNA up to 100%[32]. After that this double stranded DNA use host RNA polymerases and make SSRNA. This RNA goes to host ribosome and produce different type of protein like capsomeres (it is important for capsid), some type of antigen (for put of surface), RNA polymerases, some types of DN A polymerases and so other many enzyme[34].

And all these component goes to Golgi or endoplasmic reticulum for further modification. Golgi apparatus packed all component in many types' vesicles[35]. These packed proteins will be use later for next generation virous. Like RNA dependent RNA polymerases make more and more viral SSRNA (daughter) by using mother SSRNA templet[33]. These newly make SSRNA, RNA polymerases, surface antigen, varies type of enzyme make more and more daughter SSRNA virous. And these new virous come out of liver cell by rupture the host liver cell and damage the cell, attack another new liver host cell[40].

on the other hand, in transcription process make also pregenomic RNA stand. This stand use to make double stand pDNA with the help of viral reverse transcriptase enzyme. Finally, this double stand viral pDNA make generation[38].

These new generation come out by rupture the host cell. Thus, the host liver cell is lysis continuously. And cell lysis occurs cell death[40].

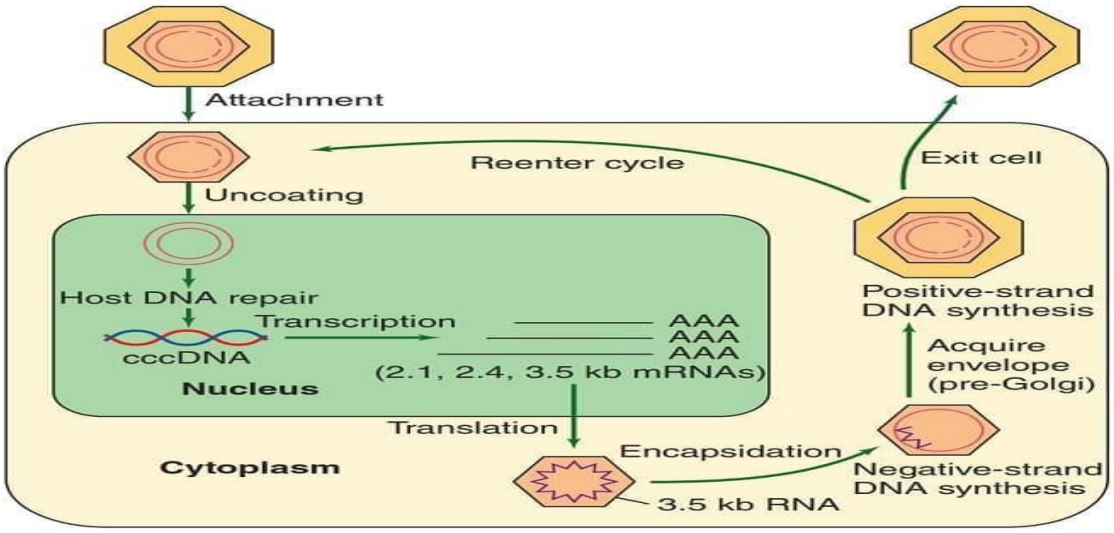


Figure of hepatitis pDNA virous [40]

Pathophysiology :

Prodromal Phase.

When liver damage it produce specific types of cytokines. These cytokines are interleukin 1, interleukin 2, tumor narcotic factor alfa, interleukin 6 (IL-1, IL-6, TNF-ALFA)[41][42]. these cytokines go to circulation from circulation go to nervous system. After that they trigger specific prostaglandin process in the brain[42]. This prostaglandin is PGE2, PGF2. this prostaglandin changes the hypothalamic thermostat and leads to a fever. This is the general discomfort of the body[43].

When liver cell continuously dies due to damage of liver that time toxins increasing in the blood. These hepato toxin accumulate and inter into brain through blood. In brain they goes to brain steam specially chemo trigger zone[42]. This zone are very very sensitive to hepato toxin. This hepato toxin act on some receptor and activate this zone.

This chemo trigger zone further activate another structure like emetic center .this emetic center activate a nerves which goes to gastrointestinal tract and that cause retro peristaltic action action. This reverse peristaltic action leads to vomiting and nausea[42][43].

This vomiting leads to dehydration. And dehydration leads to fall blood pressure and loss of many electrolytes. If this condition occurs for many days its leads to weight loss.so these are common symptoms of hepatitis[42]. Not only this hepatotoxin change peristalsis movement in upstream, it changes also downstream. In this case it creates diarrhea. These all are prodromal phase[43].

Ectaric Phase

In site of liver cell unconjugated bilirubin react with some enzyme like uridine glucuronic transferase and covert into conjugated bilirubin. But in phase 2 maximum liver cell are die, liver loss the ability to covert[44][45]. For this reason increase concentration of unconjugated bilirubin and conjugated bilirubin in blood. On the other hand, biliary system licks some enzyme and material in to blood due to over all damage of liver like bile acids. When unconjugated bilirubin, conjugated bilirubin, bile acids accumulate high amount that move to some tissue and accumulate into that tissue. When accumulate into eye tissue eye covert yellowish color eye[44].

When these components accumulate in to thick skin like palms of hand and soles of feet it gives discoloration. Normally convert yellowish color palm and soles. That is jaundice like effect[44].

When conjugated bilirubin and unconjugated bilirubin amount high in blood it goes to kidney for filter but kidney only can filter conjugated bilirubin. When kidney handle high concentration conjugated bilirubin that time kidney produces dark urine [45].

When liver and biliary system will damage due to hepatitis less amount bilirubin goes to gut. This less amount bilirubin convert less amount euro bolenogen by bacteria. This less amount euro bolenogen convert into less amount sterco billin. And we know this component are responsible for yellow color of stool. For less amount this component stool converts into clay or pale color stool[44][45].

Due to liver and biliary system damage more, blood come to liver and inflammation will occur. That time liver will be large and inflame. The total size of liver will be increase more than previous size. And this inflammation also pain[44].

Diagnosis of viral hepatitis:

Serology of hepatitis B virous

We know hepatitis B virous contain envelope. So that virous contain surface antigen. That present on envelope surface[48]. Short form of this antigen is HBAg. when this antigen positive is one person it means that person is affected. Hepatitis B virous also contain envelope antigen and it present between envelope and capsid[49]. If it positive in one person it means two things. One is virus stay on replicating stage and another is increase infectivity. And short form of antigen is HBEAg.

Viral capsid also contain antigen. These antigens called hepatitis B core antigen. But we do not measure these antigens we measure only antibody against them. Short form of this antigen is HBCAg[48][50].

HBSAg : (+) Infection

HBEAg : (+) replicating

(+) Infecting

HBCAg : Not measure directly measure by antibody

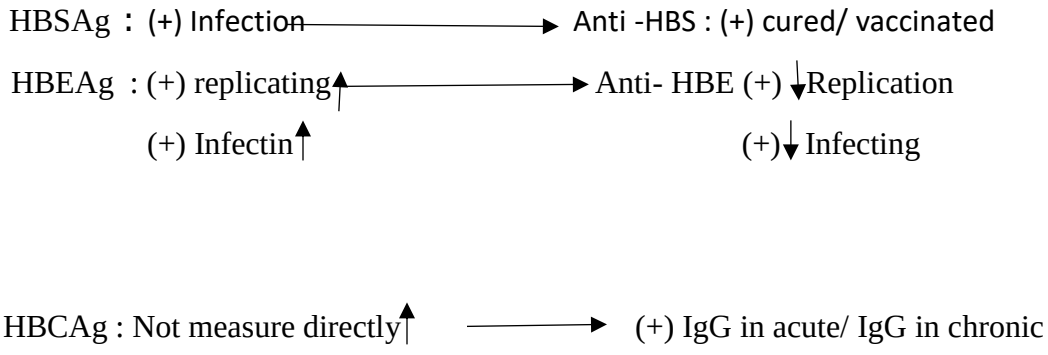
HBv DNA : (+) Replicating

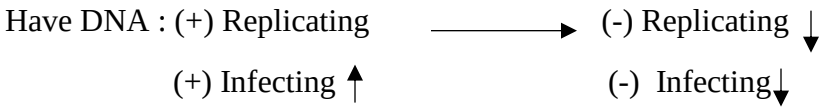
(+) Infecting

Against this antigen our body produce some antibody. Like the antibody against the hepatitis B surface antigen (anti-HBS)[51]. If its positive means patient is cure or vaccinated. The antibody against the hepatitis B core antigen called Anti- HBC in short. This antigen produces against hepatitis b core antigen. In acute condition produce IgM and in chronic condition produce IgG. Mainly IgM convert into IgG in chronic condition[52].

Last things if antigen produce against the HBCAg called the antibody against the hepatitis b envelope. In short call Anti-HBE. If it positive it means decrease replication and decrease infectivity[51].

All condition in chart[51][52] **:**





Antigen	**Antibody**
HBSAg(+)	Anti-HBSAg(-)
HBEAg (+)	Anti-HBE (-)
HBV DNA (+)	Anti-HBC (+) IgM (+)

In acute condition[51] :

Antigen	Antibody
HBSAg(-)	Anti-HBSAg(+)
HBEAg (-)	Anti-HBE (+)
HBV DNA (-)	Anti-HBC (+) IgG (+)

Recovery patient condition[51] :

Antigen	Antibody
HBSAg (-)	Anti-HBSAg(+)
HBEAg (-)	Anti-HBE (-)
HBV DNA (-)	N/A
HBCAg (-)	Anti-HBC (-) IgG (-) IgM(-)

Vaccinated/Immunize patient condition surface antigen only (HBSAg) . for that reason, body should only produce anti hepatitis B surface antibody (Anti-HBSAg)

Vaccinated patient condition[53]:

If patient do not go recover with in 6 months. That time patient will go chronic infection this is dangerous condition for patient and treatment.

Chronic patient condition (replicating stage)[51]:

Antigen	Antibody
HBSAg (+)	Anti-HBSAg(-)
HBEAg (+)	Anti-HBE (-)

HBCAg (+)	Anti-HBC (+) IgG (+) IgM(+)

Chronic patient condition (nonreplicating stage)[51] :

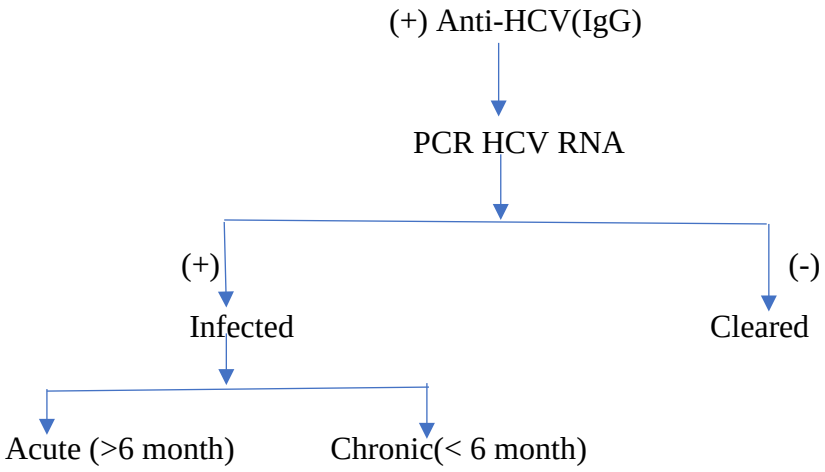
Antigen	Antibody
HBSAg (+)	Anti-HBSAg(-)
HBEAg (+)	Anti-HBE (-)
HBV DNA (+)	N/A
HBCAg (+)	Anti-HBC (+) IgG (+) IgM(+)

Serology of hepatitis c :

For this test first check blood antigen of hepatitis c virous (anti-HCV). If anti-HCV is present that time also do PCR of HCV RNA[51]. If that is not positive assume patient some how cleared from hepatitis c virous. On the other hand, PCR test is positive that time assume patient are affected by virous[52].

If it is present (RNA) less than 6 month that time called acute infection, more than 6 month called chronic infection. In case of chronic infection do liver biopsy or fibrosure text to determine amount of liver fibrosis / damage. That time done APRT test and determine the fibrosis value. if value goes to more than 1.5 that time assume a sever fibrosis occurs[53].

In short



In case of chronic infection do liver biopsy test

APRT = {(patient AST/AST standard)/platelet}⁒ 100

APRT = > 1.5 ⟶ ↑↑ Fibrosis

Serology of hepatitis D[55]:

If HBV are positive that time check the HDV infection test.

Serology for acute HDV (+)

HDV RNA(+)	IgM (+)

Serology for chronic HDV(+)

HDV RNA(+)	IgM (+)

Hepatitis A serology[55] :

Hepatitis A and normally cause acute infection. Hepatitis E virous and hepatitis C virous do not have vaccine but others hepatitis A, B, D have vaccine.

chronic condition	HAV RNA(+)	IgM(+)
Post expouse/ Immunized	HAV RNA(-)	IgG(+)

This immunized / post expoused IgG stay on blood 1/2 decades . after destroy

Hepatitis E serology[56] :

chronic condition	HAV RNA (+)	IgM (+)
Post expouse/ Immunized	HAV RNA(-)	IgG(+)

This immunized / post expoused IgG stay on blood 2/3 years, after destroy

Treatment & management:

Treatment & management of hepatitis A&E:[60]

Hepatitis A&E both are RNA virous and mostly cause acute infection. Hepatitis A&E are self-limiting disease[60][67].

- Take completely bed rest
- Must avoid physical activity
- Avoid fried and spicy diet, take light diet
- Drink clean & boiled water
- Must avoid alcohol (OH)
- As medicine can be take multivitamins like and liver tonic type medicine
- Avoid other medicine which harmful for liver

Vaccine are available for treatment of hepatitis A virous but hepatitis E vaccine is not discovering yet[60].

Treatment & management of hepatitis B&D[85]:

Hepatitis D infection occurs when hepatitis b infection already presents previously. Hepatitis D infection occurs in case, one is coinfection and other is super infection. Same time hepatitis B and Hepatitis D infection call coinfection. And when hepatitis B infection occurs first and hepatitis D infection occurs some days later of b infection[85][88].

If hepatitis B is acute than hepatitis D also acute & goes within hepatitis B infection[89]. If hepatitis B is chronic than hepatitis D become chronic and damage liver fully. So, our main target point is hepatitis B. Hepatitis D do not make disease without hepatitis B virous[90].

- Take proper bed rest & Must avoid more physical activity.
- Should take more fluid.
- Avoid other medicine which harmful for liver.
- Must avoid alcohol (OH).
- Avoid fried and spicy diet, take light diet.
- Drink clean & boiled water.

90 to 95 % hepatitis is acute (Infection less than 6 month). 5 to 10% will suffer from hepatitis B chronic infection. 15 to 20 from chronic hepatitis will suffer from cirrhosis & cancer[88].

Available & most famous drug are [99]:

- Interferon alfa
- Adefovir
- Entecavir
- Tenofovir
- Lamivudine

All this medicine reduces viral load in chronic infection case not treat 100%[90]. Liver transplant is the last option in liver damage. Hepatitis D do not have vaccine but hepatitis B vaccine are available[91].

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Treatment & management of hepatitis C[92]:

20% hepatitis C is acute means resolve within short time (less than 6 month). 80% hepatitis C is chronic means lasts for long time. Once hepatitis C become chronic than there is chance of cirrhosis or cancer[93]. Ratio is very low & it take years to damage liver[94].

- Avoid fried and spicy diet, take light diet.
- Drink clean & boiled water.
- Take proper bed rest & Must avoid more physical activity.
- Must avoid alcohol (OH).
- Avoid other medicine which harmful for liver and should take more fluid.

Available & most famous drug are [99]:

- Interferon alfa
- Ribavarin
- Ombitasvir
- Paritaprevir
- Dasabuvir

Anti hepatitis medication & mechanism[99]:

For hepatitis B virous[99]

1. Reverse Transcriptase inhibitors

- NRTI'S

  - Lamivudine ○ Entecauir
  - Tenofovir disoproxil fumara
  - Emtricitabine
  - Tenofovir alafenamide

NTRTI'S ○ Adefovir ○ Tenofovir NRTI'S NRTI'S means nucleoside reverse transcriptase inhibitors and NTRTI'S means nucleotide reverse transcriptase inhibitor. Basically, they act on hepatitis B reverse transcriptase enzyme and stop production of virous[101].

Mechanism of reverse revers transcriptase inhibitors

To understand mechanism of reverse revers transcriptase inhibitors at first will understand how hepatitis B virous infect liver cell[100] . hepatitis B virous is a DNA virous. This virous attack the liver cell and go into cell by endocytosis or other mechanism and disappear all structure accept pDNA . After that this pDNA inter into nucleus that time DNA repair enzyme come and repair the hole double stranded DNA up to 100%[102]. After that this double stranded DNA use host RNA polymerases and make SSRNA. This RNA goes to host ribosome and produce different type of protein like capsomeres (it is important for capsid), some type of antigen (for put of surface), RNA polymerases, some types of DN A polymerases and so other many enzyme[103].

And all these component goes to Golgi or endoplasmic reticulum for further modification. Golgi apparatus packed all component in many types' vesicles. These packed proteins will be use later for next generation virous. Like RNA dependent RNA polymerases make more and more viral SSRNA (daughter) by using mother SSRNA templet[104]. These newly make SSRNA, RNA polymerases, surface antigen, varies type of enzyme make more and more daughter SSRNA virous. And these new virous come out of liver cell by rupture the host liver cell and damage the cell, attack another new liver host cell[105]. On the other hand, in transcription process make also pregenetic RNA stand. This stand use to make double stand pDNA with the help of viral reverse transcriptase enzyme. Finally, this double stand viral pDNA make genaretion. These new generation come out by rupture the host cell. Thus, the host liver cell is lysis continuously. And cell lysis occurs cell death[104].

Now this reverse transcriptase inhibitors act on revers transcriptase enzyme for this reason this enzyme can not do its work properly as a result double stranded DNA is not make from ssRNA[107]. tase When reverse transcriptase enzyme read the template RNA stand and add nucleotide in that time this drug act as false nucleotide. these drugs do not contain OH group for this reason they do not from hydrogen bon d between 2 nucleotides (template RNA nucleotide and false drug nucleotide). For this result reverse transcription process terminate[108] .New daughter virous are not produce due to unpresents of pDNA although all viral functional and nonfunctional protein are produce NRTI'S and NtRTI'S both are reverse transcriptase inhibitors but NRTI'S is

nucleoside reverse transcriptase inhibitors and NtRTI'S is nucleoside reverse transcriptase inhibitors , both they act as a false nucleotide[106].

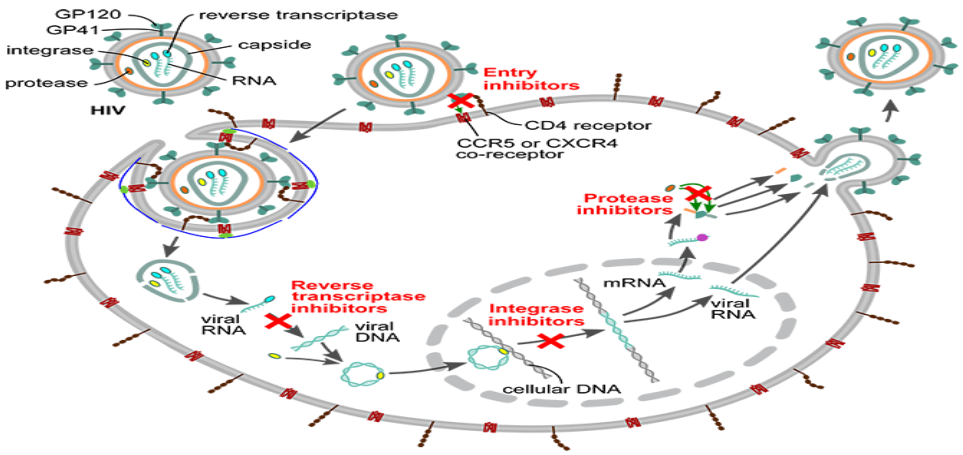


Figure : IFN-ALFA mechanism [107]

Mechanism of INF- alfa

When liver cell injured by virous in that time they release many camicals , alfa inter feron one of them. These components go to another unfacted cell and bind specific receptor. After bind with receptor activate secondary signal mechanism and express some specific gene[107]. These gene produce some special peptide. These peptides do not give to work virous properly. At first, they stop the production of viral protein synthesis, they do not give convert viral ssRNA to viral DNA, they express some protein out site of the cell (MHC-1 COMPLEX)[110]

- Viral protein synthesis (-)
- DNA formation (X)
- MHC-I complex formation (+)

Virous bind to MHC-I complex in that time our immune cell like CD8, CT do not bind with this complex, and as a result our immune system understand some problem there and secrete some enzyme and destroy these infected cells[111]. We can use this component as a drug. It decreases viral load by three way in hepatitis b chronic infection[112].

For hepatitis C virous [99]:

1. Protease inhibitors

- Simeprevir
- Paritaprevir
- Glecaprevir

2. NS5A inhibitors
   - Ledipasvir
   - Velpatasvir
   - Daccatasvir

3. NS5B inhibitors
   - Sofosbuvir
   - Dasabuvir

4. Ribavirin

To understand mechanism of these inhibitors and ribavirin at first will understand how hepatitis C virous infect liver cell[113][114]. hepatitis c virous is an RNA virous. This virous attack the liver cell and go into cell by endocytosis or other mechanism and disappear all structure accept RNA.This RNA goes to ribosome and make big big poly protein. This protein has 5 part, NS3 part, NS4A part, NS5A part, NS5B part. NS3 and NS4A protein are responsible for make many structural and functional protein of virous[115]. NS5A are responsible to make some type of integral protein that needs to make more RNA and also assembly of viral component. NS5B are responsible for replication of viral RNA and make more copies[116].

Mechanism of Protease inhibitors:

When viral rna goes to ribosome and produce big poly protein in that time protease inhibitors act. We know big poly protein have 5 part, NS3 part, NS4A part, NS5A part, NS5B part. NS3 and NS4A protein are responsible for make many structural and functional protein of virous[116]. That time NS3/NS4A protease enzyme act on NS3 ,NS4A part and break down , and produce viral structural and functional protein. Protease inhibitors inhibits this enzyme and do not break NS3,NS4A part of poly protein[117]. Thus, virous protein cannot do produce[116].

Mechanism of NS5A inhibitors:

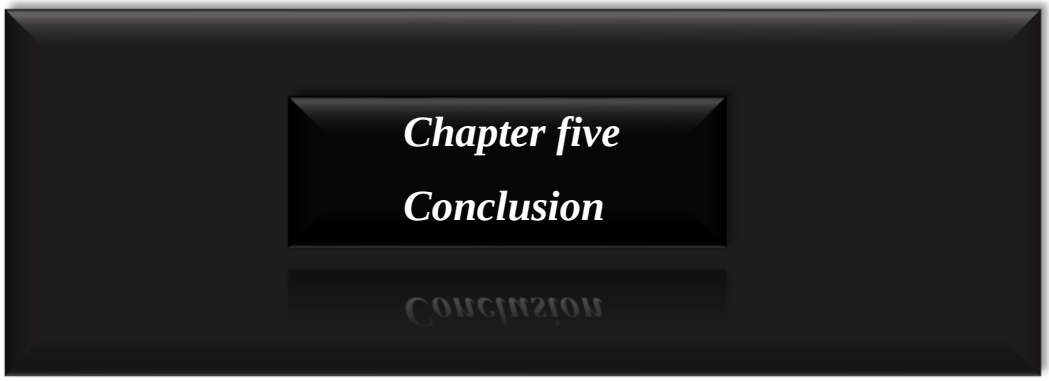
viral rna goes to ribosome and produce big poly protein in that time protease inhibitors act. We know big poly protein have 5 part, NS3 part, NS4A part, NS5A part, NS5B part. NS5A are responsible to make some type of integral protein that needs to make more RNA and also assembly of viral component. This drug inhibits NS5A protein and cannot do produce integral protein and stop viral replication

Mechanism of NS5B inhibitors:

Virous bind to many surface receptors of human liver cell and inter in to our liver cell. After that disappear its all component and express viral RNA. RNA produce polyprotein by using host ribosome. This big poly protein has 5 part, NS3 part, NS4A part, NS5A part, NS5B part. Every part has many difference functions but NS5B part have specific function. This part produces such enzyme which mainly responsible for viral RNA replication. NS5B inhibitors inhibit this enzyme and stop RNA proliferation.

Mechanism of Ribavirin[118]:

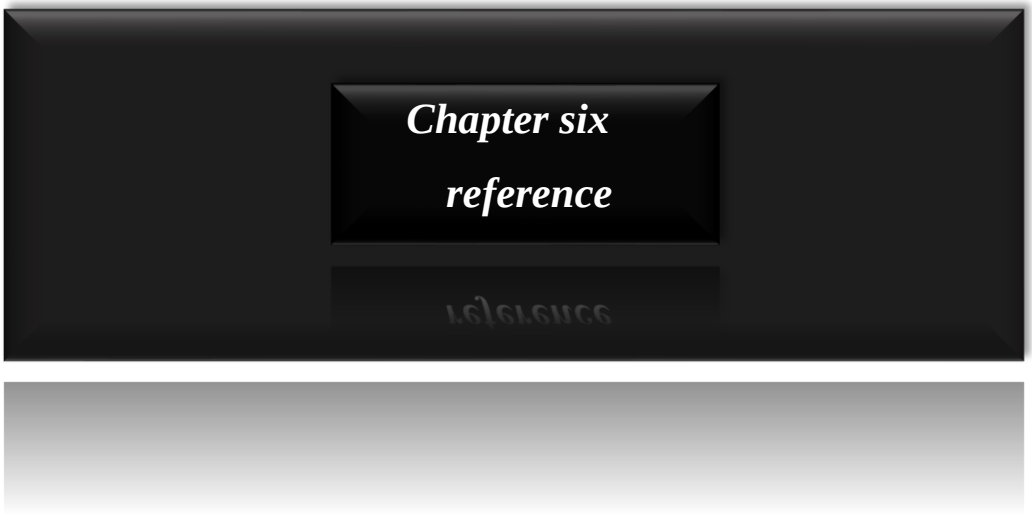
Ribavirin inhibit ionosine monophosphate dehydrogenase enzyme. This enzyme is mainly responsible for produce guanine nucleotides. For this inhibitor that enzyme cannot do its own activity and can not do make guanine nucleotide. As a result, stop viral RNA production. This drug mainly uses in refractory hepatitis c. In case of refractory hepatitis c use triple therapy 1. Ribavirin, 2. NS5B inhibitors, 3. INF- alfa



Hepatitis B and C kill about 20,000 people every year in the United States, and more than 1 million worldwide (CDC, 2013; WHO, 2016). Hepatitis B contagion(HBV) and hepatitis C contagion(HCV) together regard for utmost viral hepatitis, which kills further people every time than road business injuries, HIV and AIDS, and diabetes(WHO, 2016)[120]. While the deaths from other common killers(i.e., malaria, tuberculosis, and HIV) have dropped since the early 2000s, deaths attributable to viral hepatitis continue to rise(IHME, 2016)[121]. These deaths can be prevented. Three boluses of HBV vaccine convey 95 percent impunity(WHO, 2015). Though HBV infection can not be cured, proper treatment can reduce viral cargo to an undetectable position(EASL, 2012)[122]. While there's no vaccine for HCV, new restorative treatments can exclude the infection in over 95 percent of cases(Afdhal etal., 2014; Charlton etal., 2015; Feld etal., 2014). bettered forestallment and expanded access to viral hepatitis treatments could greatly reduce the burden of these infections[123].

The World Health Organization(WHO) estimates that reducing the prevalence of habitual hepatitis B and C by 90 percent and reducing mortality by 65 percent would save7.1 million lives by 2030(WHO, 2016)[125]. The United States has an occasion and a responsibility to be part of the global action against hepatitis B and C. formerly the Department of Health and Human

Services' viral hepatitis action plan lays out ambitious pretensions for perfecting forestallment and care, and expanding hepatitis surveillance(HHS, 2014)[126]. In the near term, the commission finds control of both conditions to be imminently possible. This commission also believes that a further ambitious thing is within our reach Elimination of HBV and HCV as public health problems in the United States[127]. Although an elimination thing is entirely doable, it isn't inescapably probably without considerable attention to the walls bandied in this report. First of all, complaint reductions programs bear an accurate understanding of the true burden of complaint in a population[128]. There's wide query in all estimates of HBV and HCV prevalence and frequence. Limited surveillance contributes to the query, as does the frequently asymptomatic course of the infections[129]. Wider webbing could help identify more chronically infected people, but screening for both infections is complicated[130].



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