HEPATITIS B AND C TREATMENT GUIDELINES FOR NIGERIA 2015

GUIDELINES COMMITTEE
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CONTENTS
1. Introduction
2. Hepatitis B
3. Who to screen
4. Management strategies
5. Treatment options
6. Monitoring and evaluation
7. Treatment response
8. Special groups
9. Prevention of Hepatitis B
10. Hepatitis C
11. Who to screen
12. Management strategies
13. Prevention of Hepatitis C

1.0 INTRODUCTION
Viral hepatitis refers to an inflammatory disease of the liver caused by viruses that have an affinity for the liver. Five viruses have been found to be clinically relevant and they are labeled A, B, C, D and E.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) have been found to be the most important causes of chronic liver disease such as liver cirrhosis and liver cancer ultimately resulting in premature death. Worldwide serological evidence of past or present infection with HBV is found in about 2 billion people. Of this number, 350-400 million are chronically infected and this results in about 1 million deaths annually.

Nigeria is an area of high endemicity for HBV with over 70% of the population showing evidence of past infection with the virus and 7.3 – 24% of the populace having serological evidence of current infection (average 13.7%). Going by the 2006 national census and an estimated current population of about 170,000,000, this translates to about 23 million Nigerians being currently infected and about 7 million of these may die of the consequences of this infection.

For HCV, the prevalence worldwide is 170 million chronically infected people. The range of prevalence of HCV infection in Nigeria is between 0.5- 4% in the general population.

The liver disease caused by the two viruses is silent and unrecognized in the early stages. The impact is often underestimated by both the sufferers and the healthcare professionals. Consequently, most patients present very late with advanced liver cirrhosis and cancer. HBV is both preventable (vaccination) and treatable if diagnosed early; currently, there is no vaccine for HCV; however, effective curative treatment is available.

1.1 Rationale for Management Guidelines:
(a) Improve awareness and appreciation for HBV/ HCV disease and management among healthcare workers.
(b) To standardize management and decision making in the approach to HBV/ HCV diseases at various levels of the health care.
(c) To adapt the criteria in management of HBV/ HCV to a resource-limited country like Nigeria.
(d) To sensitize health workers/ general populace on the prevention of viral hepatitis.
(e) To facilitate and standardize research into HBV/ HCV-related diseases.

2.0 HEPATITIS B

Hepatitis B refers to a necro-inflammatory disease of the liver caused by the hepatitis B virus (HBV). Transmission occurs vertically (mother to child), horizontally (child to child), by sexual contact, contaminated needles/ sharp objects, blood transfusion, and any contact of blood or blood products with breached skin, etc. Providing education about how to avoid risky behaviour is essential in improving prevention.

In Nigeria, most infections occur in childhood (vertical and horizontal transmission) and 70-90% of vertical infections will result in a chronic infection compared to 20-50% of early childhood infections (horizontal), which will progress to the chronic stage. In contrast, when transmission occurs in adolescents or adults, only 1-5% will progress to the chronic infection unless the individual is immunocompromised.

For a country of high endemicity like Nigeria, studies have shown that universal vaccination at birth is cost effective[Stevens CE et al (1985), Ip HM et al (1989)]. However, for children, adolescents and adults not vaccinated at birth, screening would be essential to establish HBV status. Those who are HBsAg and anti-HBc negative should be vaccinated while those who are HBsAg positive should be evaluated for further management.

Chronic hepatitis B (CHB) virus infection is a major cause of end-stage liver disease and hepatocellular carcinoma. The term ‘Chronic’ is applied to the disease because of the ability of the virus to persist beyond 6 months in the body and pose a lifelong threat of liver cirrhosis and hepatocellular cancer. This emphasizes the need for regular monitoring of patients for disease activity.

3.0 WHO TO SCREEN?

Nigeria is a hyper-endemic country for HBV. All Nigerians are, therefore, at risk and should be counseled and screened for HBV infection at any available opportunity.

Opportunities for screening include:
- Any visit to hospital/ clinic
- Pre-school entry
- Pre-employment assessment.
- Pre-insurance
- Pre-marriage counselling
- Pregnancy & antenatal clinic booking
- Blood / organ donation.
- Contact with identified cases.

* Healthcare workers, emergency care workers and law enforcement/ military personnel are at a particularly high risk of acquiring HBV infection and those vulnerable should be screened routinely.

Screening tools-screening tools include hepatitis B surface antigen (HBsAg), antibodies to the surface antigen (anti-HBs) and antibody to the core antigen (anti-HBc).

Recommendation:
HBsAg should be used for general screenings since it is more easily available.

All positive subjects require further evaluation for treatment by a Gastroenterologist or an appropriately trained and certified physician.

All negative subjects should be evaluated for vaccination (using anti-HBc & anti-HBs)

3.1 Patients and Other Individuals/ Conditions to be Prioritized for HBV Screening:
- Abnormal liver function tests (LFT) especially elevated ALT of unknown cause.
- Haemoglobinopathies with frequent blood transfusions.
- Patients who develop jaundice or increased aminotransferases after blood transfusion.
Patients with cirrhosis or suspected hepatocellular carcinoma (HCC).
- Spouses or children or siblings of HBsAg positive persons
- HIV positive patients.
- Chronic renal failure (CRF) patients, especially if haemodialysis is planned.

3.2 Further Evaluations to be Carried Out For All HBsAg Positive Individuals:

3.2.1 Clinical Evaluation
(a) History- Alcohol use, traditional herb use, cigarette smoking, risk factors for co-infection with HIV, family history of liver related death, etc.
(b) Features of advanced chronic liver disease: Jaundice, weight loss, hepatomegaly or shrunken liver, splenomegaly, asterixis, bleeding tendencies, spider naevi, gynaecomastia, distended anterior abdominal veins, testicular atrophy, breast atrophy, brittle hair, female hair distribution in males, fluid retention, parotid swelling, palmar erythema, erythema on soles, finger clubbing, leuconychia.

3.2.2 Laboratory Diagnosis
Phase 1- Initial evaluation for HBsAg positive subjects (mainly asymptomatic patients)
(a) Viral markers: IgM anti-HBc, IgG anti-HBc, HBeAg, anti-HBe, anti-HBs, anti-HDV*, anti-HCV, anti-HEV*, anti-HAV*, HIV screening.
(b) Assessment of hepatic injury/severity: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, prothrombin time (PT), ultrasonography.
(c) Full blood count (including platelet count).
(d) Liver imaging - Ultrasound to determine features of possible advanced liver disease and hepatocellular carcinoma (HCC).
(e) Molecular biology: HBV DNA viral load assessment

Phase 2 - Patients who are symptomatic, negative for IgM anti-HBc or have abnormality of any of the Phase 1 investigations.

(f) Non-invasive tests such as APRI score of greater than 2, FIB-4 or Fibrosan score greater than 11kPa [APRI = (AST/ ULN) x 100/ Platelet count (10^9/L); FIB-4 = (Age in years) x AST (IU/ L)/ Platelet count (10^9/L) x ALT½] * May not be necessary or routinely available

(g) Liver biopsy with special stains including: Masson's trichrome (fibrosis), orcein (elastin fibers, HBsAg), Periodic acid Schiff-diastase (alpha-1 antitrypsin deficiency), reticulin (fibrosis, collapse, HCC), Perls' iron (haemosiderin and iron products) immunohistochemistry for HBsAg, HbcAg, HDAg, AFP, copper (Wilson's disease).

Liver biopsy findings should be categorized into mild, moderate or severe chronic hepatitis B or, better still, semi-quantitatively scored by a scoring system like the Knodell Histological Activity Index (HAI). Comments about degree of fibrosis should also be included.

3.2.3 Categorization of Subjects After Evaluation
Based on the findings of the evaluation above, subjects may be categorized into the phases: as shown in Figures 1 and 2.

4.0 MANAGEMENT STRATEGIES
4.1 Pre-treatment Counselling:
It is important that patients are fully informed in simple terms about the following in order to improve compliance:
- The health implications of chronic hepatitis B infection.
- The chronic nature of the disease - monitoring and treatment may be lifelong.
- The possibility that spouse(s), children and close relatives may be infected and the need to screen them.
- The need to avoid further health risks such as alcohol and traditional herbs.
**Table 1: Differentiation of chronic hepatitis B infection**

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>Liver histology</th>
<th>HBV-DNA</th>
<th>HBe antigen</th>
<th>Anti HBe</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerance</td>
<td>Normal or minimally elevated</td>
<td>Normal or Mild activity, no fibrosis</td>
<td>&gt;20,000 IU/ml (&gt;10^6 copies/ml)</td>
<td>Positive</td>
<td>Negative</td>
<td>*Monitor</td>
</tr>
<tr>
<td>Immune clearance (HBe)</td>
<td>Elevated/active (fluctuating positive CHB)</td>
<td>Active</td>
<td>&gt;20,000 IU/ml (&gt;10^6 copies/ml)</td>
<td>Positive (most of the time)</td>
<td>Negative</td>
<td>Treat</td>
</tr>
<tr>
<td>Inactive (HBeAg carrier state)</td>
<td>Persistently normal#</td>
<td>Inactive, usually with minimal fibrosis</td>
<td>#Low, or undetectable &lt;2000 IU/ml (&lt;10^4 copies/ml)</td>
<td>Negative</td>
<td>Positive</td>
<td>Monitor</td>
</tr>
<tr>
<td>Reactivation (HBe-negative CHB)</td>
<td>Elevated/often fluctuating</td>
<td>Active with variable amounts of fibrosis</td>
<td>Moderate, often fluctuating, &gt;2000 IU/ml (&gt;10^4 copies/ml)</td>
<td>Negative</td>
<td>Positive</td>
<td>Treat</td>
</tr>
</tbody>
</table>

*Normal ALT is regarded as less than three quarters (75%) of the laboratory's upper limit for males and less than half (50%) for females.

*Treatment may be considered in certain individuals in this phase (e.g., individuals with family history of HCC, health workers in direct contact with patients and Nigerians aged ≥30 years).

#For a definitive diagnosis of inactive CHB to be made, the ALT must be persistently normal and HBV DNA persistently <2,000 IU/ml in tests done every 3 months for 12 months.

- The financial implications of treatment options in relation to the desired goal of treatment.
- Potential side effects of the treatment options should be discussed.
- The objectives and likely outcomes of treatment should be discussed in terms of virological response, normalization of liver functions and prevention or reduction in the risk of further liver damage and liver cancer.

**HBeAg negative**
- HBV DNA viral suppression
- ALT normalization
- Loss of HBeAg and development of anti-HBs

### 4.2 Goals of Treatment - General Objectives:
- To eliminate or significantly suppress HBV replication
- To prevent liver disease progression to cirrhosis, liver failure and liver cancer
- To prevent transmission of HBV infection.
- To improve quality of life.

### 5.0 TREATMENT OPTIONS

(a.) Tenofovir (Tdf)
(b.) Entecavir (ETV)
(c.) Pegylated interferon alpha 2a (PEGSYS®)
(d.) Telbivudine (TBV)
(e.) Adefovir dipivoxil (ADV)
(f.) Lamivudine (LAM)

Currently the standard of care is to use the nucleos(t)ide analogues with high barrier to resistance such as Tenofovir or Entecavir, or if indicated, Pegylated interferon-α. The oral drugs with low barrier to resistance (e.g., LAM) are to be avoided as much as possible.
Fig. 1: Algorithm of diagnostic workup

Hepatitis B and C Treatment Guidelines

Asymptomatic subject

Screen for HBsAg

HBsAg +ve

- IgM positive (acute infection – no treatment). REPEAT HBsAg test after 6 months. If positive do HBeAg, ALT & HBV DNA

Anti-HBc (IgM/Total)

- IgM Negative/Total Positive

- HBeAg
- ALT
- HBV DNA

- Negative

No biopsy, serial monitoring

- Positive

Liver biopsy

- Minimal/ mild CH

Follow up

- Moderate/ severe CH

Treat

HBsAg -ve

No action

Immunize

Negative

IgM Negative/Total Positive

Screen for HBsAg

HBsAg +ve

No biopsy, serial monitoring

IgM positive (acute infection – no treatment). REPEAT HBsAg test after 6 months. If positive do HBeAg, ALT & HBV DNA

HBsAg -ve

Positive

Immunize

Negative

No action
Fig 2: Algorithm for patient management
### Table 2: Comparative analysis of treatment options for HBV in Nigeria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>300mg daily p.o.</td>
<td>Well tolerated; potent HB viral suppression; effective against wild type and lamivudine resistant HBV; no record of HBV resistance</td>
<td>Risk of nephrotoxicity; monitoring of renal function needed</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5mg daily p.o.</td>
<td>Well tolerated; potent HB viral suppression; low rate of HBV resistance at 2 years (18% at 2 years)</td>
<td>Higher cost; No long-term data in HBV infection; less effective in some lamivudine resistant HBV strains</td>
</tr>
<tr>
<td>Pegylated IFN</td>
<td>180mcg wkly s.c for 48 weeks</td>
<td>Very favorable response rates in both HBeAg -ve and +ve disease; finite treatment duration; more durable HBeAg seroconversion; greater likelihood of HBsAg loss in HBeAg positive and negative disease; no resistance.</td>
<td>Tolerability; less favourable safety profile (many side effects); high cost; parenteral (subcutaneous) administration</td>
</tr>
<tr>
<td>Adefovir</td>
<td>10mg daily p.o</td>
<td>Well tolerated in advanced liver disease; effective against wild type and lamivudine resistant HBV; low rate of HBV resistance in first 2 years</td>
<td>Higher cost; resistant HBV mutants in 29% after 5 years. Nephrotoxic at higher doses</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>600mg daily p.o.</td>
<td>Well tolerated; renoprotective</td>
<td>Moderate anti-viral activity and low drug resistance (20% in 4 years)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>100mg daily p.o.</td>
<td>Well tolerated; safe in decompensated liver disease; more affordable and widely available</td>
<td>Less durable HBeAg seroconversion; potentially life threatening ALT flares on iscontinuation of therapy; resistance in 70% of cases after 5 years therapy</td>
</tr>
</tbody>
</table>

### Table 3: Treatment of patients with compensated cirrhosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Remarks</th>
<th>Therapeutic End-Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PegIFN</td>
<td>Monitor HBV DNA every 3 months for the first 1 year; thereafter, every 6-12 months until HBV DNA becomes undetectable. Regression of fibrosis and even reversal of cirrhosis can occur. HCC surveillance is mandatory.</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Treatment is indefinite*; if there is HBeAg loss with anti-HBe seroconversion, give 12 months of consolidation therapy and then stop</td>
</tr>
<tr>
<td>Entecavir</td>
<td></td>
<td>Treatment is indefinite*; therapy may be stopped only if there is HBsAg loss and anti-HBs seroconversion</td>
</tr>
</tbody>
</table>

*Duration of therapy with Peg IFN is 48 weeks. All adults, adolescents and children with chronic hepatitis B and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg or HBV DNA levels using the nucleos(t)ide analogues. The patient with decompensated cirrhosis should, in addition, be referred for evaluation for liver transplantation.*
Subjects under treatment for CHB should be monitored for the following:

**Oral Nucleos(t)ide Analogues**
1. Serum ALT– every 3-6 months until HBV DNA becomes undetectable; thereafter annually
2. HBV-DNA – 3-6 monthly until HBV DNA becomes undetectable; thereafter annually.
3. HBe antigen and anti-HBe – every 6 months till seroconversion
4. Serum electrolytes, Ca$^{2+}$, PO$_4^{2-}$, urea and creatinine – every 3 months for a year, and if they remain normal, every 6 months thereafter

**Pegylated Interferon-alpha**
1. Serum ALT - every 4-8 weeks
2. HBV DNA - 12 weeks, 24 weeks, 48 weeks & 72 weeks
3. HBeAg and anti-HBe - every 6 months till seroconversion
4. Full blood count (including platelet count) - every 4-8 weeks
5. HBsAg quantification - 12 weeks, 24 weeks, 48 weeks & 72 weeks

**7.0 TREATMENT RESPONSE FOR PEGYLATED INTERFERON**
- For HBeAg positive CHB patients, if the HBV DNA is not less than 20,000 IU/ml and no decline in Hepatitis B surface antigenaemia from baseline at 12 weeks treatment should be stopped

**8.0 SPECIAL GROUPS**

1. **HBV/HCV co-infection**
   - Co-infection with HCV is associated with a more severe disease and rapid progression to both liver failure and HCC.
   - **Treatment** - treatment must be for the dominant infection while monitoring the latent one. The dominant infection is the one with the greater viral load. Latent infection may flare up after the dominant infection has been successfully treated. If this occurs, it should be treated according to this guideline.

2. **HBV/HIV co-infection**
   - HIV infection worsens the liver disease in HBV infected persons and is also associated with rapid progression to end stage liver disease.
   - **Treatment** - simultaneous treatment of both diseases usually required. The preferred drug combinations include Tenofovir + Emtricitabine (or Lamivudine) in combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI), usually efavirenz or protease inhibitor.

3. **HBV/HDV co-infection**
   - HDV co-infection is also associated with rapid progression to end stage liver disease. A high index of suspicion is required if the serum HBV-DNA is low and the ALT is high.
Diagnosis is based on the presence of anti-HDV, HDV-RNA, or immunohistochemical evidence of delta antigen in the liver.

**Treatment - use IFN (conventional or pegylated) - for 12 - 24 months**

4. **Pregnancy**
   Standard care is to immunize the infant within 12 hours of delivery with Hepatitis B immunoglobulin (HBIG) and Hepatitis B vaccine. However, there are reports that indicate that treatment of pregnant women with either HBeAg positivity or high HBV-DNA levels in the last trimester with nucleoside analogues (e.g. tenofovir or telbuvudine or lamivudine) reduces the risk of intra-uterine and perinatal transmission of the virus.

5. **Chemotherapy (cancer patients) and immunosuppressive therapy (including transplant patients)** - Reactivation of HBV infection may occur in this situation and may be accompanied by fatalities. Chronic HBV carriers should thus be commenced on anti-HBV therapy (tenofovir or entecavir) at least one week before the commencement of the above therapy and continued for 6 months after cessation. Note that patients should be on lifelong anti HBV suppression treatment post transplant.

6. **Children**
   This category of patients is mostly in the immune tolerant phase of the disease and thus will require a longer period of observation. Indications for treatment are similar as for adults namely elevated ALT, and/or increased HBV-DNA.
   Tenofovir is used in those above 12 years and entecavir in those 3-12 years.

9.0 **PREVENTION OF HEPATITIS B**
   (1) Health education for the public and health care providers.
   (2) Universal immunization (infants, children, adolescents) and implementation of NPI scheme for HBV vaccination.
   (3) Contact tracing and immunization of non-immune persons.
   (4) Screening and vaccination of all special risk groups especially surgeons, laboratory workers, dentists, emergency workers and law enforcement agents.
   (5) Screening of pregnant women at ante-natal clinics and immunization of the non-immune. Immunization of all babies born to HBV-positive pregnant women immediately after birth as well as giving HB immunoglobulin (HBIG).
   (6) Screening of all blood/organisms and blood products before transfusion/transplantation.
   (7) Proper disposal of all sharp instruments (needles, lancets, blades, etc.)
   (8) Non-recycling of disposable instruments used in medical procedures (needles, lancets).
   (9) Sterilization of all instruments used by traditional medical practitioners for invasive procedures (e.g. circumcision, tattooing, ear piercing, etc.).
   (10) Easy availability of HB immunoglobulins for post-exposure prophylaxis.
   (11) Practice of ABC (abstinence, “be faithful” and condom) as in the prevention of HIV infection should be encouraged.

10.0 **HEPATITIS C INFECTION**
    HCV is a single strand RNA virus. Infection by HCV, just like HBV, is usually insidious and most patients are asymptomatic or suffer only a mild illness. Routes of transmission are largely similar to those of HBV namely; transfusion of unscreened blood, or blood products, organ transplant, needle stick injuries, injection drug use, unsterilized medical instruments, body piercing, tattoos/scarification, sex (relatively low risk), and shared personal items. Mother to child transmission is not as effective as in HBV infection. However, the risk for this increases in mothers who are HIV positive or who have very high HCV RNA titres in late pregnancy. About 80% of those who are infected go on to become chronic carriers for many years; 10 - 20% develop chronic liver disease including cirrhosis and a further 10% develop hepatocellular carcinoma (HCC) after 10 - 20 years.
Unlike HBV, there is no immunity after the resolution of an infection; this is thought to be due to the diversity and numerous strains of the virus. Furthermore, there are currently no vaccines against HCV.

In Nigeria, most studies on hepatitis C are not community based with the majority of reported studies among blood donors. Therefore the available data significantly under-represents the actual burden of the condition. The best estimate possible suggests the prevalence at between 0.5 - 4%.

Management of chronic hepatitis C (CHC) has been recently simplified with the advent of oral directly acting anti-virals (DAAs).

11. WHO TO SCREEN?
- Persons who have injected illicit drugs
- Children born to HCV infected mothers
- Healthcare, emergency, medical and public health workers.
- Persons at special risk: persons with hepatomegaly and/or unexplained serum ALT elevated levels, persons on haemodialysis, recipients of blood/blood products and organ transplants; HIV positive persons
- Persons with sexually transmitted infections (STI) and high risk sexual behaviour with multiple sexual partners; male homosexuals.
- Commercial sex workers
- Pregnant women

11.1 Screening Tools
1. Antibody to HCV (3rd generation ELISA recommended)
2. HCV-RNA - used for patients with HIV infection and end stage renal disease.

11.2 Investigations for HCV Positive Persons
- Confirmation (and quantification) of a positive anti HCV test using the most sensitive real-time HCV RNA (PCR) available.
- HCV genotyping.

11.3 Further Evaluations
1. Liver function tests (LFT).
2. Full blood count including platelet count.
3. Prothrombin time.
4. Liver imaging.
5. Non-invasive tests of liver fibrosis
6. Liver biopsy to determine the grade, stage and prognosis of liver disease.
7. Serological test for HBsAg, HIV and anti-HAV.

11.4 Pre-treatment Evaluation
1. Markers for autoimmune disease.
2. Thyroid function tests.
3. Assess for alcohol and drug abuse.
4. Evaluate for depressive or psychiatric illness.

12.0 MANAGEMENT STRATEGIES
12.1 Goals of Treatment
- Achieve cure by sustained virological response (SVR)
- Prevent complications of HCV infection such as liver cirrhosis and liver cancer.
- Reduce risk of transmitting infection to others.

12.2 Who should be Treated?
1. All patients who are HCV RNA positive
2. Acute hepatitis C after 12 weeks of observation with no fall in HCV RNA titres.

12.3 Contra-indications to Treatment
- Pregnancy.
- Continuing alcohol abuse.
- Severe cardiac disease.
- Uncontrolled psychiatric illness.
- Uncontrolled auto-immune disease.
- Untreated thyroid disorder.
- Under three (3) years of age.
- Uncontrolled seizure disorder.
- Severe co-morbidity e.g. severe hypertension, heart failure, poorly controlled diabetes mellitus, obstructive pulmonary disease.
- In this era of direct acting oral antiviral drugs, patients with most of the above contraindications can be treated.
Table 1: Recommended CHC treatment regimens for patients without cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Drug Combinations (including dosage)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PegIFN (180µg/ wk) + Ribavirin (1g or 1.2g/ day) + Sofosbuvir (400mg/ day)</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN + Ribavirin (RBV) + Simeprevir (150mg/ day)*</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir (SOF) + Ledipasvir (90mg/ day)</td>
<td>8 - 12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Simeprevir (SMV)</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir (60mg/ day)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>2 &amp; 3</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV</td>
<td>12 weeks (genotype 2)</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>24 weeks (genotype 3)</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN + RBV + SMV*</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Ledipasvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + SMV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>5 &amp; 6</td>
<td>PegIFN + SOF + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Ledipasvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Continue PegIFN & RBV for 12 weeks for naïve or relapsed patients and 36 weeks for partial or null responders

Table 2: Recommended CHC treatment regimens for patients with compensated cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Drug Combination</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>PegIFN + RBV + SMV*</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + Ledipasvir</td>
<td>24 weeks#</td>
</tr>
<tr>
<td></td>
<td>SOF + SMV</td>
<td>24 weeks#</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>24 weeks#</td>
</tr>
<tr>
<td>2 &amp; 3</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>SOF + RBV</td>
<td>16-20 weeks (for G2 only)</td>
</tr>
<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>24 weeks#</td>
</tr>
<tr>
<td>4</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>PegIFN + RBV + SMV*</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>SOF + Ledipasvir</td>
<td>24 weeks#</td>
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<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>24 weeks#</td>
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<tr>
<td>5 &amp; 6</td>
<td>PegIFN + RBV + SOF</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>SOF + Ledipasvir</td>
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<tr>
<td></td>
<td>SOF + Daclatasvir</td>
<td>24 weeks#</td>
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*Treatment may be extended for another 12 weeks for partial or null responders

#Duration of treatment may be reduced to 12 weeks with the addition of ribavirin (RBV)
12.4 Treatment

HCV treatment is rapidly evolving. The aim of treatment now is cure in most patients, manifested by sustained viral response. There are predictors of poor response that should be taken into account. Some of these are the genotype and subtype, the experience with previous medications (mainly partial and null responders to interferon based therapy) and those with heterozygote gene on interleukin 28G.

The current standard of care is the use of all-oral therapy. However, in Nigeria, due to the prohibitive cost and unavailability, there may be need for Pegylated interferon in combination with DAAs. Duration and dosage of therapy depend on the genotype, stage of liver disease of the patient, previous response to treatment and presence or absence of predictors of poor response. Some of these drugs are effective in all genotypes while others are more limited. The simplest regimens at present are given in Tables 1 and 2.

From above it is clear that the combination to remember most is that of Peg IFN + Ribavirin + Sofosbuvir for 12 weeks. It is effective in all genotypes and in patients with or without compensated liver disease, and in both those who are interferon/ribavirin naïve or experienced. When DAAs only are to be used, Sofosbuvir and Daclatasvir for 12 weeks in patients without cirrhosis and either for 24 weeks alone or combined with Ribavirin for 12 weeks in those compensated cirrhosis.

Patients with decompensated cirrhosis are treated while waiting for liver transplantation, and post transplantation to minimize possibility of relapse in the allograft. There are many other recommended regimens for use, some include up to four or more drugs, so only the simplest combinations are given above.

12.5 Monitoring response

(1) HCV-RNA is assessed at initiation of therapy and at 12 weeks for genotypes 1, 4, 5 and 6. Treatment may be discontinued if patient does not achieve early virological response (i.e. more than 2 log drop or 100 fold reduction in viral load). Patients, who achieve early virological response (EVR), should have viral loads assessed at 24 and 48 weeks. For patients who have an end of treatment response, the sustained virological response (SVR) should be assessed at 24 weeks after cessation of therapy. However, for all-oral therapy, HCV RNA should be done only at baseline and 12 weeks post therapy.

For genotype 2 and 3, on interferon based therapy, HCV-RNA should be assessed at initiation of therapy and at 4, 12 weeks for rapid and early virological response. End of treatment response should be assessed at the end of 24 weeks and SVR assessed 24 weeks after cessation of treatment.

(2) Monthly haematological and biochemical profile.

(3) Three (3) monthly thyroid function test.

(4) Monthly evaluation for depression.

12.6 Adverse Effects of Drug Therapy for Interferon Based Treatment

(1) Flu-like syndrome (fever, chills, headaches, myalgia) which is self-limiting and can be controlled by anti-pyretics/analgesics, e.g paracetamol.

(2) Fatigue, weight loss, anorexia, diarrhoea, alopecia.

(3) Haematological derangements- anaemia, thrombocytopenia, neutropenia.

(4) Psychiatric disorder- mood changes, depression, insomnia, suicidal ideation, psychosis.

(5) Metabolic abnormalities – glucose intolerance, thyroid disorders.

(6) Lung complications-pneumonitis, pneumonia.

(7) Dermatological problems – various skin rashes, pruritus.

(8) Eye complications – retinal haemorrhages, retinal arterial and venous occlusion.

The DAAs have minimal side effects, and these are mainly gastrointestinal that are rarely severe enough to lead to cessation of therapy.