Guidelines for the Treatment of Chronic Hepatitis B and C Viral Infections in Kenya

Gastroenterology Society of Kenya

Republic of Kenya

Editorial Note

Both acute and chronic hepatitis cause significant morbidity and mortality in sub-Saharan Africa. Over the years, it has only been possible to offer patients preventive and supportive care. Fortunately, during the last 10 years, effective therapies have emerged for chronic hepatitis especially HBV and HCV. The field is growing quite rapidly with new classes of drugs being brought into the market every six months or so.

Due to the rapid development, the situation has become confusing for most clinicians especially in determining when to start treatment, how to follow treated and untreated patients, when to stop treatment and the optimal therapies to use.

The Gastroenterology Society of Kenya, therefore, found it necessary to develop guidelines for practicing clinicians in Kenya, who treat HBV and HCV. These guidelines contain brief notes on the clinical picture and presentation, diagnosis and currently recommended treatment in our region for both HBV and HCV. The authors have taken into account the fact that Kenya has limited resources for healthcare.

These guidelines are not meant to be utilized as a textbook on hepatitis but as a quick reference tool for clinicians. Where further reading may be required, appropriate references have been suggested.

It is hoped that these guidelines will be updated frequently.

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Foreword

Hepatitis B and C Viruses cause significant morbidity and mortality worldwide. Chronic hepatitis B afflicts more than 350 million individuals globally. The highest burden of disease is in Sub Sahara Africa and Eastern Asia (predominantly third world countries). Kenya, as classified by the World Health Organisation is a highly endemic area with a prevalence of more than 8%.

Chronic Hepatitis B has many complications, foremost among them being liver cancer (*Hepato cellular carcinoma*). In Kenya, up to 60% of chronic liver disease and 80% of Hepatocellular carcinoma is due to chronic infection with the Hepatitis B virus. Liver cancer is among the top 10 commonest solid tumours in Kenya and diagnosis with liver cancer is invariably fatal.

Transmission of these viruses in areas of endemicity is mainly through mother to child transmission. Other known routes include parenteral and sexual transmission. Hepatitis B virus is 100 times more infectious than the HIV virus and 30 times more infectious than the Hepatitis C virus.

The Hepatitis B vaccine was introduced in the early 1980s, and in Kenya, it was incorporated into the expanded program of immunisation in 2002. The vaccine has a protection rate of approximately 95%. As the vaccine was introduced worldwide in the 1980s, most of the adult population born prior to this time were not immunised and stand the danger of being chronic carriers. Some of these patients will eventually develop chronic liver diseases and hepatocellular carcinoma.

Ninety percent (90%) of patients with Hepatitis C will develop complications of chronic liver disease: liver cirrhosis, liver failure and hepatocellular

carcinoma. Currently, there is no vaccine available for Hepatitis C virus and nearly all who suffer this infection will eventually need treatment.

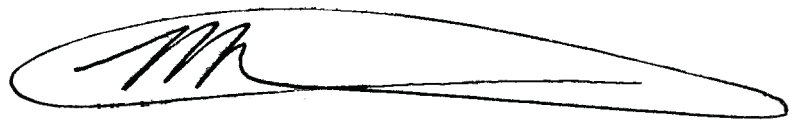
Over time several treatment modalities for Hepatitis C have been developed. The success rates and dosing of the drugs are some of the associated complexities. Recent advances in therapy have made available new drugs that have a shorter treatment course, better tolerance and higher response rates. This leads to improved clinical outcomes in these patients.

Over the last 30 years, there have been developments in the treatment options for both chronic Hepatitis B and C. Decisions on who to treat, how to treat and when to treat have been diverse and left the majority of doctors including those in Kenya unsure of how to manage these patients.

The Gastroenterology Society of Kenya in collaboration with the Ministry of Health has found it necessary to address the burden of this disease by formulating clinical practise guidelines to standardise and optimise the care of Chronic Hepatitis patients.

These guidelines were specifically formulated for Kenya, however, we are certain that they are suited for use in the wider Sub Sahara African region where no such guidelines exist.

A lot of effort has gone into the development of these guidelines. I therefore urge all practitioners to make good use of them in order to reduce morbidity and mortality from Chronic Hepatitis thus contributing to the development of the human capital necessary for the achievement of Vision 2030.



Dr. Francis Kimani
Director of Medican Services

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These guidelines are as a result of hard work and support from various people and organizations.

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We appreciate the commitment by members of the Editorial Board who spent a lot of their time writing and discussing various chapters of the guidelines.We hope that the guidelines will adequately address the gap they were intended to fill.

Finally we extend our gratitude to all those who in one way or another participated in the preparation of this publication be they, staff of Roche Pharmaceuticals or members of the Editorial Board.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
cccDNA	Covalently closed circular DNA
CHB	Chronic Hepatitis B
CMV	Cytomegalovirus
D4T	Stavudine
DDI	Didanosine
EBV	Ebstein Barr virus
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HSV	Human simplex virus
IV	Intravenous
MSM	Men who have sex with men
SVR	Sustained virologic response

General Introduction

Hepatitis is a general term referring to inflammation of the liver. Viral hepatitis refers to hepatitis resulting from a variety of different viruses such as Hepatitis A, B, C, D and E.

Chronic hepatitis remains a significant health problem in Kenya; the region being classified as a high prevalence zone. Morbidity and mortality rates are high and this is compounded by low disease awareness, absence of treatment protocol and the virulent nature of the disease itself.

This guideline seeks to standardize the care of chronic hepatitis patients among the Kenyan population with a view to optimizing outcomes as measured by morbidity and mortality associated with the disease.

It provides a guide based on current scientific evidence and recommendations on aspects of the management of hepatitis whilst balancing individual patient factors and adaptability to our local setting.

Chronic Hepatitis B

Introduction

The hepatitis B virus is a DNA virus that causes both acute and chronic disease. The pathological consequences of persistent Chronic Hepatitis B include the development of chronic hepatic insufficiency, cirrhosis and hepatocellular carcinoma (HCC) (1). Hepatitis B virus can be classified into seven genotypes A to G based on nucleotide divergence (2).

Burden of Disease

Epidemiology

The rate of Chronic HBV infection varies from 0.1 to 20% in different areas of the world (3). It is estimated that one third of the world's population (approx. 2 billion people) have been infected with Hepatitis B at some point in their lives and of these 350 – 400 million people are chronically infected. Every year about 600,000 - 1,000,000 people die from hepatitis related disorders (2).

The prevalence of HBV is particularly high in sub-Saharan Africa and accounts for over 80% of the adult patients with sporadic hepatitis.

Studies in Kenya have shown a prevalence rate of HBsAg of 8.8% but values in urban areas range from between 8% - 30% (4; 5; 6; 7; 8). In one of the studies 34% of those positive for HBsAg were children aged between 5 and 10 years (8).

In patients with HCC over 70% are positive for HBsAg (8). Hepatocellular carcinoma is the fifth commonest solid tumour among the Kenyan population. In a study looking at the different types of liver cancer in Kenya 80% were Hepatocellular Carcinoma, 8% cholangiocarcinoma and two percent hepatoblastomas mainly in children (8).

Table 1: Serological markers in Chronic Hepatitis B

Name	Abbreviation	Definition
Hepatitis B surface antigen	HBsAg qualitative HBAg quantitative	The antigen marker that indicates infection Acts as a predictor of response
Hepatitis B virus deoxyribonucleic acid	HBV DNA	Indicates active viral replication
Alanine Aminotransferase	ALT	Liver enzymes increased in liver cell inflammation
Hepatitis B core antibody	Anti HBc	Indicates previous (IgG) or an on-going infection (IgM)
Hepatitis B surface antibody	Anti HBS	Usually indicates immunity
Hepatitis B e Antigen	HBeAntigen	Correlates with HBV replication and infectivity but is absent in patients with pre core or core mutations
Hepatitis B e Antibody	HBeAb	Indicates seroconversion - a treatment end point

Screening Criteria

Kenya being a high prevalence area for HBV(> 8% prevalence as per the World Health Organization) screening should be offered to all. For screening purposes the recommended test is HBsAg. Routine screening is recommended for the following high risk populations (9; 10):

1. Infants born to infected mothers
2. Health care workers
3. Haemodialysis patients
4. I.V drug users
5. High risk sexual behaviour
6. HIV positive patients

Evaluation of the Patient

Clinical Evaluation

a. History

i) High risk populations e.g. health care workers, high risk sexual behaviour, pregnant women ante natal screening, patients undergoing dialysis, transfusion, transplant recipients, patients with symptoms of liver disease.

ii) Other considerations are patients with history of alcohol use, family history of liver disease

b. Physical

Patients with features of liver disease such as jaundice, weight loss, small liver span, splenomegaly, ascites, bleeding tendency, flapping tremors, testicular atrophy and other stigmata of chronic liver disease should be subjected to laboratory testing to confirm diagnosis and status of liver disease.

It is important to exclude atypical features such as: arthritis, kidney abnormalities, and bone marrow abnormalities.

Laboratory Evaluation

a. Priority Tests

   i) Liver Function tests

   ii) Serological markers: HBsAg, HBeAg, HBeAb, IgM and IgG anti HBc

   iii) Viral load: HBV DNA +/- Quantitative HBsAg levels

   iv) Other Tests: HIV, HCV, Alpha Feto Protein levels, coagulation profile, +/- liver biopsy

b. Imaging

   i) Liver ultrasound

   ii) Fibro scan where available

Categorisation of the Patient

Diagnosis and appropriate management of patients with chronic hepatitis B requires accurate separation of patients into different categories. The different groups reflect different phases/stages in the natural progression of the disease. However, the phases are not necessarily sequential (11).

The main parameters in this categorisation include:

1. Serological markers
2. Alanine Aminotransferase (ALT)
3. HBV DNA (viral load)
4. Presence and level of necro-inflammation on histology

Factors that influence the progression of the natural history of chronic hepatitis B include:

1. Gender
2. Age of infection
3. The host immune status
4. Viral mutations
5. Hepatitis B e antigen status
6. Alcohol use
7. Co-infection with HCV or HIV

The different phases of progression include the following:

1. The Immune Tolerant Phase

Characteristics

i) HBeAg positive
ii) High levels of viral replication (high serum HBVDNA)
iii) Normal ALT
iv) Minimal or no hepatic necro inflammation
v) No or slow progression to liver fibrosis
vi) Chances of spontaneous HBeAg loss is low

2. The Immune Clearance Phase (HBeAg positive CHB)

Characteristics

i) HBeAg Positive
ii) Low levels of viral replication (low serum HBVDNA)
iii) Elevated ALT
iv) Severe necro-inflammation and rapid progression of fibrosis
v) If immune clearance successful, then sustained HBeAg sero-conversion with development of anti-HBe occur.

3. *Inactive HBV Carrier state (Latent Phase)*

Characteristics

i) Results from HBeAg sero-conversion to anti HBe

ii) Very low viral load (serum HBVDNA) <2000 IU/ml to undetectable levels.

iii) Normal ALT

iv) Good prognosis, much lower risk of progression to liver cirrhosis and HCC.

v) HBeAg loss and sero-conversion to anti-HBs occur spontaneously at a rate of 1-3% per year.

4. *Reactivation Phase*

About 5-15% of individuals in the inactive phase develop HBeAg negative chronic hepatitis B. More common in older individuals as a marker of chronicity. Mutations (nucleotide substitutions in the pre-core and/or basal-core promoter regions of the HBV genome) result in HBV variants that are unable to express HBeAg while HBV continues to replicate.

Characteristics

i) HBeAg negative

ii) Elevated levels of ALT

iii) High HBV DNA levels

iv) Significant necro-inflammation

v) Progress to fibrosis and HCC

It is important to distinguish latent phase from this reactivation phase. This can be achieved by a one year follow up of individuals with 3-4 months ALT and HBV DNA levels. Individuals in the inactive phase may also revert back to HBeAg positive.

Occult HBV Infection

Individuals who have cleared HBsAg but have detectable plasma HBV DNA usually have very low levels <200 IU/ml.

Serology

1. HBsAg Negative
2. HBsAb Positive
3. Anti HBc IgG Positive

While no liver disease is associated with occult infection these individuals are at risk of reactivation of HBV with immune suppression and require prophylactic antiviral therapy.

Chronic HBV Progression

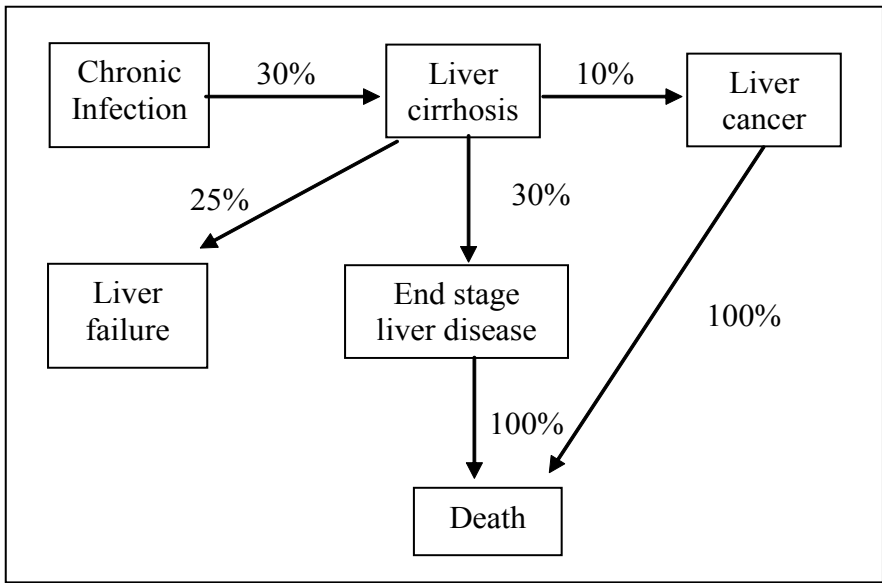

Figure 1: Schematic representation of chronic HBV progression

Goals of Treatment

The treatment goals in patients with chronic HBV are to:

1. Reduce the risk of progressive chronic liver disease,
2. Prevent transmission to others,
3. Prevent long-term complications such as cirrhosis and hepatocellular carcinoma and death

Several studies have evaluated the impact of treatment for chronic HBV on the risk of HCC. Systematic reviews of the available data suggest that the relative risk is reduced by approximately 50 to 60 percent following treatment with interferon or nucleos(t)ide derivatives. Treatment does not however, completely eliminate the risk, and the benefit was not seen in patients who developed nucleos(t)ide resistance (12).

Treatment of Chronic Hepatitis B

The following information is required in determining a patient's eligibility for treatment.

1. Alanine aminotransferase (ALT) levels
2. HBeAg status
3. HBV DNA levels
4. +/- Liver biopsy when indicated
5. +/- HBsAg serum levels (quantification)

It is important to classify Chronic Hepatitis B according to the 'e' antigen status to decide on therapy as below:

HBeAg positive:

HBeAb Negative - treat at HBV DNA > 20,000 IU/ml

HBeAg negative:

HBeAb positive treat at HBV DNA >2000 IU/ml

Who to Treat

For HBeAg positive patients, treat when:

1. HBV DNA > 20,000 IU/ml and if:

- ALT > 2ULN: Commence treatment without liver biopsy.
- ALT 1-2 ULN: Do liver biopsy and treat if shows moderate to severe necro-inflammation
- ALT normal and age >40years: Follow up with 3-6 monthly ALT. If two consecutive ALT levels are elevated >2 ULN then treat, however if they remain >1-2 ULN then do a liver biopsy.

Do not rely on a single ALT reading to make the decision. Serial ALT measurements are recommended.

2. If HBV DNA <20,000 IU/ml:

- Normal ALT: No treatment, Monitor ALT & HBV DNA every 6-12 months.

Treatment decision is made based on the results of the ALT and HBV DNA.

For HBeAg Negative Patients, treat when:

1. HBV DNA ≥ 2000 IU/ml and

- ALT >2 ULN: Treat: No liver biopsy needed.
- ALT < 2 ULN: Monitor ALT 3-6 monthly or consider liver biopsy.

No treatment:

- HBV DNA <2000 IU/ml. (Inactive carrier)
- ALT normal: Monitor ALT and HBV DNA every 6-12 months.

Who Not to Treat

- Immunotolerant Individuals:

  Characterized by: HBeAg positive,
  Young <40yrs,
  Normal ALT,
  High HBV DNA >20,000 IU/ml:

- Those >40yrs should be monitored with ALT every 3-6months and if ALT is persistently >1-2 ULN then do liver biopsy and if there is moderate to severe necro-inflammation then treat (13).
- Inactive HBsAg carriers (HBeAg –ve, ALT- normal, HBV DNA < 2000IU/Ml).

Note:
Do liver biopsy if status not clear whether inactive carrier or has e-Ag chronic HBV liver disease (moderate to severe disease).

The following clinical categories require treatment:

- Active Chronic Hepatitis B
- Liver Cirrhosis (Both compensated and decompensated)
- Patients with HBV and are to undergo Immunosuppressive therapy
- Pregnant women who are HBsAg positive and high viral load (>10^7 Iu/ml)

Treatment End Points

Complete eradication of HBV from host hepatocytes cannot be achieved with currently available agents because of the persistence of HBV covalently closed circular DNA (cccDNA).

The main goal of treatment for Chronic HBV infection is ***THUS***: To halt the progression of liver inflammation to fibrosis, Cirrhosis or Hepatocellular carcinoma (11; 12).

Surrogate markers of therapeutic efficacy include:

i) Reduction of HBV DNA to undetectable level: Virological response

ii) Loss of HBeAg with or without appearance of anti-HBe: Serological response

iii) Reduction of ALT to normal levels: Biochemical response

iv) Reduction of liver necro-inflammation, with or without improvement on liver histology

v) Loss of HBsAg from serum and appearance of anti-HBs. This would be the optimal end point, but rarely achieved (11; 13).

Which Treatments to Give?

Worldwide, the following 7 agents are recognized for management of chronic hepatitis B (CHB) (14).

5 Nucleos(t)ide analogues and 2 Immuno-modulating drugs

Nucleos (t) ide analogues include:

- Lamivudine
- Adefovir
- Telbivudine
- Entecavir
- Tenofovir

NB: Lamivudine, adefovir, and telbivudine not recommended due to resistance.

Immunomodulating drugs include:

- Peginterferon alfa - 2a
- Peginterferon alfa – 2b

We recommend Tenofovir and entecavir as the preferred choices for nucleos(t) ide analogues

The recommended first line therapies for Chronic Hepatitis B are:

1. Peg interferon
2. Entecavir
3. Tenofovir

In all cases, where there exists no contraindication, the drug of choice should be Pegylated interferon.

However, in limited resource settings oral antiviral agents can be recommended as first line therapy.

Ideally the choice of peginterferon should be on the basis of individual probability of response and age: Cases of low probability should be considered for nucleos (t) ide analogue therapy first.

In addition nucleoside analogue are the treatment regimens of choice in the following:

i) Patients with hepatic decompensation,

ii) Those receiving chemotherapy,

iii) Immunocompromised patients,

iv) Pregnant patients that require therapy

v) Patients with contraindications to peg interferon (e.g. psychiatric disorders, cardiovascular diseases, thyroid disorders)

The choice will depend on indication, contraindications, availability, affordability and patient preference after educating the patient on the available recommended agents. Also to be considered is presence of HCV, HIV & Hepatitis D co-infection.

Lamivudine would also be recommended for interventions intended for <6months.

Treatment Duration and Dose

Pegylated Interferon

Dose and Duration:

- 48 weeks
- Pegylated interferon alpha 2a 180ug SC weekly
- Pegylated interferon alpha 2b as per body weight 15ug/kg SC weekly

Monitoring Tests:

TBC, LFTs, (bilirubin, Albumin, ALT), Renal function (U/E/Cs, creatinine), Thyroid function before starting treatment, then monitor at week 2, 4, 12, 36 & 48.

HBV DNA quantification, HBsAg quantification, & HBeAg/anti-HBe status before treatment then:

- HBV DNA every 3 to 6months
- HBsAg levels at week 12 and 24 if on interferon therapy
- HBeAg/anti-HBe status every 6months.

Stopping Therapy:

Consider stopping pegylated interferon:

1. If at 24weeks HBV DNA has dropped by < $2\log_{10}$ IU/ml & or if HBsAg is>20,000 IU/ml.
2. In eAg negative if HBsAg has not dropped by < $2\log_{10}$ by week 24 of treatment (14)

The second line treatment for failure of interferon therapy is **tenofovir or entecavir.**

Nucleos(t)ide Analogues:

Dose and Duration:

- Tenofovir: 1 tablet (300mgs PO) daily possibly for life

Monitoring therapy:

- Initially every 3 months for the first one year and subsequently 6 monthly thereafter.

The following investigations are recommended where resources are available.

- Liver biochemistry every 3 months
- HBV DNA 6 monthly (Tenofovir, Entecavir) 3 monthly (Lamivudine)
- HBeAg/anti-HBe: 6 monthly
- HBsAg levels 6 -12 monthly

HBeAg Positive:

- If there is seroconversion (HBeAg –ve & +ve anti-HBe): Stop 12 months after seroconversion.
- But in cirrhotics continue treatment until HBV DNA –ve by PCR and there is loss of HBsAg (13)
- Consider lifelong treatment for cirrhotics (13)

HBeAg Negative:

- Treat indefinitely.
- Stop drugs if achieves undetectable HBV DNA & HBsAg seroconversion
- But switch drug if at 48weeks still has detectable HBV DNA

Table 2: Comparison between pegylated interferon and nucleos(t)ide analogs (15)

Peginterferon	**Nucleos(t)ide Analogues**
Advantages	***Advantages***
Finite duration	Daily oral dosing
No antiviral resistance	Potent HBV DNA suppression on treatment
Response more durable post-therapy vs. nucleos(t)ide analogues	Minimal adverse events in the short term
Increase in HBsAg seroconversion rate vs. nucleos(t)ide analogues with 1 yr of treatment	Generally safe and effective in patients with advanced liver disease and hepatic decompensation
	Less expensive during first year, possibly equally or more costly than peginterferon with long-term therapy
Disadvantages	***Disadvantages***
Frequent adverse events	Risk of resistance (albeit very low to date with currently recommended first-line agents)
Weekly subcutaneous injections	Limited HBsAg seroconversion rate
Less effective on-treatment HBV DNA suppression	Response mostly not durable post therapy
Expensive	Long-term or indefinite therapy may be required

Table 3: Circumstances where a certain first line anti-HBV agent may be preferred over others (3)

Setting	Anti-HBV Agent
Decompensated cirrhosis	Tenofovir may be appropriate
Renal insufficiency	Entecavir preferred (with dose modification)
Pregnancy, woman of child-bearing age planning pregnancy in the near term	Tenofovir preferred
Woman of child-bearing age wishing to eradicate virus prior to pregnancy	Peginterferon alfa-2a or Peginterferon alfa-2b
HIV coinfection	Tenofovir plus emtricitabine or lamivudine

Treatment of Special Groups

Pregnancy

HBsAg positive & HBV DNA >10^7 Iu/ml: Consider treatment with Tenofovir, Lamivudine or Telbivudine commencing at 28 weeks. Tenofovir is the most preferred.

Third trimester treatment reduces risk of HBV transmission.

All infants of HBsAg positive mothers to receive appropriate HBIG + vaccination at birth (16).

Suggested Treatment for Immunosuppressive or Cancer Chemotherapy

Screen patients for HBV infection prior to start of immunosuppressive or cancer chemotherapy.

Who to Give Antiviral Therapy?

- All HBsAg positive patients regardless of baseline HBV DNA/ ALT

Start as soon as possible and continue until six months after chemotherapy, but 12 months if rituximab used or longer if baseline HBV DNA >2000 Iu/ml.

Which Drugs?

First line therapy:

- Tenofovir or Entecavir

  Lamivudine accepted if HBV DNA <2000 Iu/ml and planned treatment duration <12months

Suggested Treatment Protocol in Haemodialysis or Renal Transplant Patients

a) Vaccination

Give hepatitis B vaccination in HBsAg negative, anti HBs negative patients with end stage chronic kidney disease.

There is however insufficient response to HBV vaccination in patients with end stage renal disease. This could be improved by administering double dose with intensified time schedule 40µg HBsAg at 0,1,2 and 6 months as

recommended by the Center for Disease Control and Prevention (17; 18). Preferably give 20μg in each deltoid muscle.

With regard to HB Vaccination it is currently recommended to maintain anti - HBsAg antibody titres at > 100mIu/ml (10 times higher than with normal population), to achieve adequate seroprotection in haemodialysis patients (17; 18).

b) Drug Treatment

- Pegylated interferon (not in end stage) or nucleos(t)ide analogue can be used in renal impairment.
- Entecavir is recommended as 1st line oral therapy in patients with kidney disease.
- Lamivudine is good but its problem is development of resistance on long term use, thus monitor by HBV DNA.
- Adjust dose of nucleos(t)ide analogue if creatinine clearance is < 50mls/min.
- Pegylated interferon should be avoided in haemodialysis and renal transplant patients because of risk of rejection.
- Although Entecavir and Tenofovir are more effective and safer in dialysis patients, long term empirical data are very limited on these drugs.

c) Drug prophylaxis

- All HBsAg positive patients who are to undergo renal transplant should receive anti HBV prophylaxis with a nucleos (t) ide analogue. This is started just at time of transplant (at least a week before) and continued indefinitely, so long as the patient is still on immunoprophylaxis
- Entecavir is the preferred 1st line nucleos(t)ide analogue, because it offers high antiviral potency and thus low risk to resistance. Adjust dose in patients with glomerular filtration rate <50ml/min.
- Tenofovir can be used in renal transplant patients as an alternative but the renal parameters must be monitored.

- Lamivudine is safe but problem is development of resistance on long term us. It could be considered in patients with HBV DNA <2000 Iu/ml. When used monitor HBV DNA (3monthly). If rising, change to entecavir or tenofovir.
- Patients with HBV DNA >2000 IU/ml. should be started on preferably entecavir, or tenofovir if entecavir cannot be used / unavailable.

d) Who is at higher risk of reactivation

- Males
- Age >50years
- Anti HBs negative

When to Refer

Treatment of chronic Hepatitis B should preferably be done in consultation with a gastroenterologist.

Hepatitis B Vaccination and Prevention

HIV is transmitted via the following routes:

1. Sexual contact
2. Through blood and blood products
3. Sharing of contaminated needles
4. Vertical transmission

Prevention of Transmission

Measures to be taken include:

1. Practice protective sex
2. Avoid sharing intravenous drug paraphernalia
3. Immunize at risk individuals
4. Wear gloves when exposed to blood or body fluids

5. Clear up blood or body fluids using water and detergent
6. Ensure surgical instruments are disposable or adequately sterilized
7. Handle sharps safely
8. Wear goggles if there is risk of infected material splashing into the eye
9. Do not permit healthcare workers who are positive for hepatitis B e-antigen (HBeAg) to work in areas where they could be of risk to others
10. Screening of blood for transfusion against Hepatitis B virus

Immunization

- Hepatitis B vaccine is safe and effective, but should not be seen as an alternative to a strategy of prevention of transmission.
- There is also a combined vaccine available which provides protection against Hepatitis A and Hepatitis B.

Vaccination should be offered to all non-exposed Kenyans though special emphasis should be given to high risk populations.

Immunization Schedule

1. Hepatitis B vaccine is part of KEPI immunization and is given at 6,10,14 weeks.
2. The standard course of immunization in others involves the injections at 0, 1 and 6 months.
3. An accelerated course of 0, 1 and 2 months is possible. Also for combined hepatitis A and B vaccines.
4. Adults who need protection very quickly (e.g. within 48hours of exposure) can have schedule of 0, 7 and 21days. After an accelerated course, a booster at one year is recommended.
5. The duration of protection provided by Hepatitis B vaccine is still unknown.

6. It is quite possible that a course may give lifelong immunity. However it is recommended that individuals at continuing risk of infection should be offered a single booster dose vaccine once only, around five years after primary immunization. Measurement of hepatitis B surface antibody (anti-HBs) levels is not required either before or after this dose.

Testing for Hepatitis B Surface Antibody Following Immunization

- Testing for anti-HBs routinely is not recommended.
- Testing is recommended for those at risk of occupational exposure (particularly healthcare and laboratory workers).
- Antibody titres should be checked one to four months after the completion of a primary course of vaccine.
- Individual workers should know if they have been protected this information allows appropriate decision to be made concerning post-exposure prophylaxis (PEP) following known or suspected exposure to the virus.
- Antibody responses to hepatitis B vaccine vary widely between individuals.
- It is preferable to achieve anti-HBs levels above 100mlU/ml. However, levels of 10mlU/ml or more are generally accepted as adequate to protect against infection.
- Responders with anti-HBs levels greater than or equal to 100mIU/ml do not require any further primary doses. Further assessment of antibody levels is then not indicated. They should then receive the reinforcing booster dose at five years.
- Responders with anti-HBs levels of 10-100mlU/ml should receive one dose of vaccine at that time. Following this, further assessment of antibody levels is not indicated. They should then receive the reinforcing booster dose at five years.
- An antibody below 10mlU/ml is classified as a non-response to vaccine and testing for markers of current or past infection is good clinical practice. In non-responders, a repeat course of vaccine is recommended followed by retesting one to four months after the second course. Those who still have anti-HBs below 10mlU/ml, and

have no markers of current or past infections, will require hepatitis B immunoglobin (HBIG) for protection if exposed to the virus.

- Testing is also recommended in patients with chronic renal failure on dialysis.
- The role of immunological memory in patients with chronic renal failure or renal dialysis does not appear to have been studied, and protection may persist only as long as anti-HBs levels remain above 10mlU/ml.
- Antibody levels should be monitored annually and if they fall below 10mlu/ml, a booster dose of vaccine should be given to patients who have previously responded to the vaccine.

Booster doses should also be offered to any haemodialysis patients who are at a high risk of exposure if they have previously responded to the vaccine particularly if they are to receive haemodialysis and have not received a booster in the preceding 12 months.

Hepatitis B Immunoglobulin

- Specific hepatitis B immunoglobulin (HBIG) provides passive immunity.
- It can give immediate but temporary protection
- HBIG is given concurrently with hepatitis B vaccine and does not affect the development of active immunity.
- If the injection occurred at the time of immunization, administration of HBIG may still prevent the development of carrier status.

Post Exposure Management

- Post exposure prophylaxis (PEP) involves giving hepatitis B vaccine and possibly immunoglobulin too if required.
- Immunoglobulin is given at different site and it does not reduce the immune response to the vaccine.
- If the status of the source is not known assume infection.
- PEP may be indicated even if the exposed person has received hepatitis B vaccine previously.

- It should be given within 48 hours and certainly not later than seven days after exposure.
- The incubation period of the disease is 40 to 160 days.
- If the site of exposure is a "needle stick" injury, cut or abrasion, the site should be washed immediately with soap and water
- t is indicated for babies born to mothers who are chronic carriers of hepatitis B virus or to mothers who have had acute hepatitis during pregnancy.

Complications

Adverse reactions to the vaccine are few and usually mild.

- There may be some soreness and erythema around the site.
- Fatigue, malaise and influenza – like symptoms are rare.
- An association with Guillain-Barre -type syndrome has not been substantiated.

Hepatitis B immunoglobulin is well tolerated.

Chronic Hepatitis C

Introduction

Hepatitis C refers to an inflammatory condition of the liver caused by the Hepatitis C virus (HCV). The spectrum of the disease varies from a mild illness lasting weeks to a chronic lifelong condition that can lead to liver cirrhosis or liver cancer. Three percent of the world's population are chronically infected with HCV (1).

The principal routes of transmission include;

- Blood and blood products
- Unsafe surgical or medical procedures,
- Parenteral transmission via tattooing or acupuncture with unsafe materials, shared drug paraphernalia etc.

Both heterosexual and vertical transmission do occur although at significantly lower rate than HBV/HIV

There are six HCV genotypes numbered 1 to 6 with a number of subtypes that have been described for some of the genotypes.

In Kenya the commonest genotypes are 4 and 1 with genotype 4 being the commonest genotype.

Burden of Disease

Epidemiology

Worldwide, up to 200 million individuals are currently chronically infected (3), with HCV and are at risk of developing cirrhosis and HCC as a result of persistent infection. It is one of the 10 leading causes of infectious disease deaths worldwide causing 250000 deaths per year (19). Recently HIV and HBV co-infection have added to the burden of disease leading to higher morbidity and mortality.

In Africa, prevalence varies between 0.6-18% with countries in North Africa having higher incidence rates that those in sub-Saharan Africa (20). Work done in Kenya shows the prevalence of HCV in blood donors is between 1.5-2.5% with higher values in IV drug users up to 30% (21; 22). It is now estimated that intravenous drug use accounts for 80% of acute HCV infections (3). HCV accounted for 2.8% of chronic liver diseases in a study carried out in KNH in 1996, but newer data is urgently needed (23).

Screening of Chronic Hepatitis C

Who and When to Screen

Everybody should be screened; however it is highly recommended that the following groups of people must be screened where routine screening is not possible;

- Patients donating blood or blood products for transfusion
- Haemodialysis recipients and staff
- Healthcare workers and those exposed to blood
- Intravenous drug users

- People with risky sexual behaviour (MSM – Men who have sex with Men, bisexual, multiple sexual partners)
- Immuno compromised patients (such as HIV positive, renal transplant patients and patients on chemotherapy)
- Accidental injuries (needle stick injury, shared razor blades, tattoo clients)
- Individuals with pre-existing liver diseases

Evaluation of an HCV Patient

Clinical Evaluation

a) History

Detailed history of the patients' symptoms should be taken; such symptoms include general malaise, fatigue, joint aches, headaches, fever, jaundice, change in urine colour, pruritus and history of transfusions or other risky behaviour.

b) Examination

Clinical evaluation should be thorough and should include signs of acute and chronic liver disease

Occasionally, patients present with complications of non-target organs such as kidney and joint diseases.

Laboratory Investigations

a) Laboratory Tests

Biochemical tests including liver function test such as bilirubin, AST, ALT should be done and repeated after 2 weeks. HCV infection should be confirmed by antibody assays, followed by quantifying the HCV RNA

(viral load). For prognostication and decision on therapy duration, the genotype has to be determined. These are genotype 1 to 6. In addition it's important to know the renal and thyroid function.

b) Imaging

Ultrasonography/ fibro scan of the liver is useful in rough estimation of liver damage.

Note: although not mandatory liver biopsy should be done for disease impact and treatment follow up.

Patients should be screened for other viruses such as HBV/HAV/HIV (in some areas it might be important to consider HEV, EBV, CMV, and HSV).

Who to Treat

Treatment should be offered to a patient adequately counselled in:

- Drug information
- Duration of treatment
- Prognosis
- Cost
- Side effects
- Prognosis

All patients who are positive for HCV and have raised LFTs should be offered treatment.

Contra-Indication to Therapy

- Depression, psychosis, epilepsy
- Uncontrolled autoimmune disease

- Pregnancy
- Couples unwilling to comply with adequate contraception during and six months after treatment
- Poorly controlled hypertension, diabetes, heart failure and chronic obstructive lung disease
- Low haemoglobin, low neutrophil count of less than 1500/mm3, platelet count less than 90000/mm^3, creatinine more than one and half times normal
- Untreated thyroid disease

Treatment Goals

The rationale for treatment in patients with chronic HCV is to:

- Reduce the risk of progressive chronic liver disease
- Prevent transmission to others
- Prevent other long-term complications such as cirrhosis and hepatocellular carcinoma and death

The goal of antiviral therapy in patients with chronic HCV is to eradicate HCV RNA, which is predicted by attainment of a **sustained virologic response – SVR (absence of HCV RNA by PCR 6 months after completing treatment).**

A SVR is associated with a 97 to 100 percent chance of being HCV RNA negative during long-term follow-up and attaining an SVR has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications, even among those patients with advanced liver fibrosis. Several viral, patient, and treatment related factors influence a patient's chance of eradicating the virus.

Important predictors of treatment response include:

- **HCV genotype** (genotypes 2 and 3 are more responsive to treatment than genotypes 1 and 4)
- **Baseline viral load** (≤600,000 to 800,000 IU/mL)
- **Race** (whites have higher response rates than African Americans and Latinos)
- **Host genetic factors** (e.g. IL28B polymorphisms)
- **Use of combination therapy with peginterferon and ribavirin**
- **Treatment adherence**

Drug Management of Chronic Hepatitis C

The HCV genotype should be assessed prior to treatment initiation since it influences decisions on the dose of ribavarin and on duration of treatment. Standard recommended treatment for HCV is dual therapy consisting of Pegylated interferon and ribavirin.

First-Line Treatment

Pegylated IFN-alpha 2A, Dose 180 ug SC once a week.

Or

Pegylated IFN alpha 2B, Dose 1.5 ug/kg/week SC

For genotype **1, 4, 5, 6** adjust ribavirin dose according to weight up to a maximum of 1 .2 gm daily for 48 weeks

For Genotype 2 and 3, ribavirin could be adjusted to a lower dose of 800 mg in divided doses. (For patients with BMI above 25 use Ribavirin 1.2 gm daily).

Treatment Dose Reduction and Stopping Rules

Interferon should be stopped in the following instances:

- In case of severe depression
- If absolute neutrophil counts falls below 500/mm^3
- If platelets counts fall below 25,000/mm^3

Virological Treatment Follow Up on Therapy

Changes in viral load during therapy are used to determine if a patient is responding to treatment and to predict whether the patient is likely to eradicate the virus. In general, the earlier the HCV RNA becomes undetectable during treatment, the more likely the eradication of the virus will be achieved. Several terms are used to describe the response to antiviral therapy in patients with chronic HCV infection:

- **Rapid virologic response (RVR)**: HCV RNA negativity after four weeks of treatment; if the HCV RNA remains negative at 12 weeks it is known as an extended rapid virologic response (eRVR)
- **Early virologic response (EVR)**: at least a 2 log10 reduction in HCV RNA (a partial EVR) or HCV RNA negativity (a complete EVR) by week 12 of treatment
- **Delayed virologic response**: HCV RNA negativity at week 24 in patients who fail to achieve a complete EVR (such patients are also known as "slow responders")
- **End of treatment response (EOT):** HCV RNA negativity at the end of treatment

Treatment Adherence, Supportive Care

- It is important to counsel patients on doses and the need to adhere to treatment in order to achieve good responses.
- Before starting treatment patients must be instructed about the schedule and the side effects to be expected during treatment.

- Patients should be advised how to use antipyretics and analgesics.
- Regular follow up visits are important.

Co-relation of Co-factors

Body weight (BMI) adversely affects treatment. Lowering of weight prior to treatment is useful.

Alcohol consumption should be avoided. For this, the patient will need support.

Newer Treatment

For HCV genotype 1 and 4 two first generation protease inhibitors i.e. Telaprevir and Boceprevir increase the response rate (24) when added to treatment. These may also be used in those patients who failed the first line of treatment and might soon be first line therapy for genotypes 1 and 4 (Triple therapy).

Future Developments

Many new oral drugs are in development and in the next few years one can look forward to only oral therapies with short duration of treatment. Polymerases are quite promising and drugs like **Sofosbuvir** and **Daclatasvir** have a very great promise.

When to Refer

When to refer a HCV patient to specialist with experience in the management of hepatitis:

- Patients with established portal hypertension or decompensated liver disease
- Patients with co-morbidities e.g. diabetics
- All non-responders

- Patients with complications while on treatment
- All co-infected patients
- HCV-HIV co-infection
- Cancer patients on chemotherapy
- Other special groups such as: pregnant women, paediatrics

Prevention of Hepatitis C

Currently there is no vaccine to prevent hepatitis C infection. However, you can take steps to protect yourself from becoming infected with hepatitis C virus and to prevent passing the virus to others.

Strategies:

- Do not share personal care items that might have blood on them such as razors or tooth brushes.
- Avoid injected drugs or, for drug users, enter a treatment program.
- Never share needles, syringes water or equipment for intravenous drug use and get vaccinated against hepatitis A and B if you are a drug user.
- Consider the risk of getting tattoos or body piercings. You can get infected if the tools have someone else's blood on them or if the artist or piercer does not follow good health practice.
- Do not donate blood, organs or tissue if you have Hepatitis C
- N/B HCV transmission through sex is inefficient however protective sex is recommended for discordant relationships

Chronic Hepatitis in Children

Chronic Viral Hepatitis is normally as a result of Hepatitis B or C infection. It is normally a subclinical disease and quite often asymptomatic. There is a tendency to chronicity and long term complications e.g. Cirrhosis and hepatocellular carcinoma with infections acquired in infancy and early childhood.

Chronic Hepatitis B in Children

There are very few published studies on prevalence of hepatitis B in Kenyan children. A number of sero epidemiological studies have shown high HBV carrier rates of between 3 and 15% with a high prevalence of hepatocellular carcinoma amongst the adult population. Dr. Okoth et al carried out a community based longitudinal study in Maragua and recruited both children and adults. This study was carried out between 1986 and 1987 which was before the introduction of hepatitis B vaccination into the Kenya Expanded Programme of Immunization (KEPI) schedule. An overall prevalence rate of 3% was documented. An unpublished study on prevalence of Hepatitis B amongst teenagers in high schools in Nairobi and Machakos revealed a prevalence rate of 3%.

Transmission

In highly endemic areas, perinatal transmission remains the most important cause of chronic infection because of high rates of disease in pregnant women.

HBV in childhood is acquired as a perinatal infection (vertical mother to child transmission), although horizontal transmission can occur in toddlers especially aged 5 to 7 years.

Clinical Picture

The presentation of chronic viral hepatitis in children tends to be sub clinical. The incubation period lasts one to four months. A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms, anorexia, nausea, jaundice and right-upper-quadrant discomfort. The symptoms and jaundice generally disappear after one to three months, but some patients have prolonged fatigue even after normalization of serum aminotransferase concentrations.

Signs of chronic liver disease such as ascites are rare in children and only manifest in the few who develop chronic liver disease and hepatocellular carcinoma.

In children who present with acute sporadic hepatitis, HBV accounts for less than 20% of these cases.

The progression of acute hepatitis to chronic hepatic disease, fibrosis, and cirrhosis and Hepatocellular carcinoma may take years and follows the typical course as shown below:

Table 4: Stages of Chronic Hepatitis B Progression

Immune tolerance Phase	HBV DNA levels: Increased ALT levels: Normal HBeAg status: Positive Histology: Minimal/no necroinflammation (can last up to 15 years)	Do not treat
Immune Clearance Phase	HBV DNA levels: Increased ALT Levels: Increased HBeAg Status: Positive Histology: Severe necro inflammation	Consider treatment
Chronic Inactive (latent) Phase	HBV DNA levels: Increased ALT levels: Normal HBeAg status: Negative Histology: Minimal necro inflammation (can last 10 years or more)	No treatment
Reactivation Phase	HBV DNA levels: Increased ALT Levels: Increased HBeAg status: Negative Histology: Significant necro inflammation	Treat

Investigations

Suspect Chronic Hepatitis in paediatric patients who remain HBsAg positive for more than 6 months.

The following additional tests are required:

1. HBeAg status
2. ALT levels
3. HBV DNA levels
4. HBsAg Quantification
5. Consider liver biopsy if consent is given

Drug Therapy

A conservative approach is recommended in treatment of Chronic Hepatitis B in children as experience with available drugs is not based on long term clinical trials and all available drugs are associated with occasionally severe toxicities.

First Line Therapy

a) Interferon Alpha

- Licensed for use in children > 12 months of age
- Dose: 5- 10 M units/m^2 SC three times weekly
- Duration: 6 months

Second Line Therapy

The following drugs are recommended Lamivudine /Tenofovir/ Entecavir

i) Lamivudine:

- Licensed for children ≥ 3years
- Dose: 3 mg/kg PO once daily (max 100mg/day)
- Duration: ≥ 1 year

ii) Tenofovir:

- Licensed for ≥ 12 years
- Dose: 300mgs PO once daily
- Duration: ≥1 year

iii) Entecavir:

- Licensed: ≥ 16 years
- Dose: 0.5 mgs PO once daily
- Duration: ≥ 1 year or + 6 months after HBeAg seroconversion

Interferons have limiting side effects especially haematological adverse events. However, due to the resistance that is associated with oral therapy, only offer oral therapy to children who have failed interferon therapy or are intolerant to it. Life threatening flares have been reported after stoppage of oral therapy.

Clinical trials with Pegylated interferon are on-going and this may soon be recommended for treatment once the data is published.

Chronic Hepatitis C in Children

In our setting it is a rare condition especially in infants and children although clinical data is lacking.

Prevalence in patients who frequently require transfusion e.g. sicklers has not been found to be high. Perinatal transmission can occur but is inefficient. Of the children who get the disease 20% have spontaneous resolution and

80% become chronic. It tends to run a subclinical asymptomatic course but has also been associated with cirrhosis and hepatocellular carcinoma.

Clinical Picture

The presentation is similar to that of Chronic Hepatitis B in children.

Evaluation and Drug Management

a) Laboratory

- HCV antibody ELISA
- HCV RNA (viral load)
- Liver Function Tests to be repeated every 3 to 6 months
- Genotyping
- Haematological Parameters
- Renal Function Tests
- +/- Liver biopsy

b) Imaging

- Ultrasound of the liver
- Fibro scan

c) Liver Biopsy

- Is indicated before the decision to treat is taken due to the subclinical nature of the disease

Drug Management

1st Line Therapy:

- Combination therapy with Pegylated interferon + ribavirin is the standard of care.
- Pegylated interferon alpha 2a + Ribavirin
- Pegylated interferon alpha 2b + Ribavirin

Dosage:

- Pegylated interferon alpha 2a: **180mcg/1.73m2 × Body Surface Area** (16)
- Pegylated interferon alpha 2b: **1.5ug/kg**
- Ribavirin: 15mg/kg/day in two divided doses (15)

Duration:

- The genotype determines the duration of therapy.
- For genotypes 1, 4, 5, 6: Duration of treatment is 48 weeks.
- Genotype 2, 3: up to 6 months depending on the EVR (Early Virological Response).
- Genotype 2: depending on the virological response can be treated for a shorter duration.

Co-Infections in Chronic Hepatitis

HBV and HIV Co-infection

About 70–90% of all HIV patients show evidence of past or active HBV infection. The carriage of chronic HBsAg varies geographically but ranges from 1.9% to over 40%.

Studies in Kenya report rates between 12 to 40% of HIV/HBV co-infection but it should be noted that in these studies only the HBsAg alone was tested (25).

Influence of HBV on HIV

Cohort studies suggest that HBV does not appear to influence progression of HIV.

Influence of HIV on HBV

1. Lower rates of HBeAg clearance
2. Increased serum HBV DNA levels
3. Reactivation of hepatitis in asymptomatic carriers occurs
4. Faster progression to fibrosis, cirrhosis and hepatocellular carcinoma
5. Higher morbidity and mortality rates

Screening for Hepatitis B Infection in HIV Positive Individuals

All HIV patients should be offered screening for hepatitis B as a routine. If the individual is found to be negative for the disease, then vaccination should be offered as outlined in this guideline.

If on screening the HIV positive patient is found to be Hepatitis B positive, then they should be investigated further to determine if they require treatment. *For additional information on the national protocol for management of HIV/Hep B co-infection you should refer to the Guidelines for Antiretroviral Therapy in Kenya published by the National AID/STI Control Program (NASCOP).*

Assessment of Liver Disease in HIV Co-infected Patients

Recommendations

1. In patients with chronic hepatitis/HIV infection a non-invasive test is the investigation of choice such as a liver ultrasound as the non-invasive test of choice and hepatic transient elastography (TE) (Fibro Scan™) if available.
2. A liver biopsy may be considered where there are strong medical indications and consent has been obtained from the patient.

Treatment Options for Patients with HIV-HBV Co-infection

The recommended drugs are the following:

1. For nucleos (t) ide analogs: lamivudine, Tenofovir, Entecavir
2. Pegylated interferon:
    a. Pegylated interferon alpha 2a
    b. Pegylated interferon alpha 2b

When to Treat

The cut off points for treatment are similar to those in HIV negative disease i.e.

- HBeAg positive disease: HBV DNA viral load of > 20,000iu/ml
- HBeAg negative disease: HBV DNA viral load of > 2,000iu/ml

Rational Drug Use

- Determine if both diseases require treatment.
- Determine when to treat HBV alone or HIV alone.
- Monotherapy for either virus is not recommended as it leads to rapid development of drug resistance.
- For HIV positive patients who require treatment with HAART and are HBV positive, the backbone of treatment should include 2 drugs that are active against Hepatitis B.
- For HIV positive patients who are co infected with HBV and qualify for HBV treatment but do not need HIV treatment the first line therapy offered to such patients is a 48 week course of Pegylated interferon in the usual doses.
- For HIV positive patients who are co infected with HBV and qualify for treatment of both the diseases i.e. HIV and HBV, oral drug therapy is first line for these patients. The regimen must be a TRIPLE DRUG COMBINATION with at least TWO of the drugs having activity against HBV e.g. Atripla which is a combination of Tenofovir, Emtricitabine and Efavirenz.
- The use of lamivudine as Monotherapy in any of these diseases is contraindicated.

Monitoring for Toxicities

Monitor as in HIV negative patients although more adverse effects are expected in the co-infected patients than in those who have mono infection with HBV.

Vaccination in HIV

1. All non immune individuals should be vaccinated for both Hepatitis A virus and Hepatitis B virus
2. The recommended vaccination strength is 40ug at month 0, 1, 2 and 6
3. Where possible measure the AntiHBs levels four weeks after completion of the dose
4. Where the levels of AntiHBs are <10 IU/ml then the patient should be re vaccinated with three more doses at monthly intervals with a vaccine strength of 40ug

HIV and HCV Co-infection

- Studies in Kenya still indicate low prevalence rates (between 0.5% to 1.5%) of HCV co-infection (23; 26).
- HCV associated liver disease is a major cause of mortality in HIV/ HCV co-infected individuals.
- The treatment of HCV in HIV - HCV co-infected persons may increase their tolerability to HAART.

Impact of HCV in HIV

1. HIV progression is more rapid
2. More difficult to treat. HAART responses in co-infection are reduced.

Impact of HIV on HCV

1. There is increased viral replication and severe fulminant hepatitis
2. Increased HCV replication leads to rapid necro inflammation
3. There is more and rapid progression/ development of fibrosis/ cirrhosis/ hepato cellular carcinoma

4. End Stage Liver Disease is the commonest cause of death on patients on HAART in the western world. Local data on the same is currently scanty.

Treatment of HIV/HCV Co-infection

Co-infection is treated with the standard dual therapy of pegylated interferon and ribavarin as the current treatment of choice with doses and precautions similar to those in HIV seronegative individuals.

However it should be noted that response rates in HIV/HCV co-infection tend to be lower than in HIV seronegative patients i.e. 40%.

Drug Toxicities and Interactions During Treatment of HBV or HCV

Oral Therapy for HBV

(Nucleosides and Nucleotides) The drugs recommended in Kenya for oral treatment of HBV include **lamivudine, tenofovir and entecavir.**

Oral medications have minimal side effects e.g. gastrointestinal but long term side effects are still unknown with the majority of them.

Nucleoside analogs are cleared by the kidneys and appropriate dosing should take into account creatinine levels.

Nucleotides including adefovir and tenofovir have higher rates of renal toxicities and patients on long term therapy should be carefully monitored with BUN and creatinine.

Fanconi syndrome has been associated with the use of Tenofovir.

Bone mineral density decrease in patients with Tenofovir has been reported in HIV positive patients and should be monitored in patients on HBV therapy.

Long term entecavir use has been associated with possible carcinogenesis but this is still under evaluation.

Telbuvidine is associated with myopathy in long term use but local experience with this drug is very minimal.

Interferon Therapy (HBV/HCV)

Interferons have numerous side effects especially during the initial weeks of therapy. Most of the symptoms are self-limiting and reassurance of the patients is often adequate.

In those on pegylated interferons, regular biweekly total blood counts are necessary during initial management (3 months) and there-after at least every 3 months.

The major side effects of interferons are as highlighted below;

1. Anaemia
2. Neutropenia, absolute neutropenia ($<0.55 \times 10^3$)
3. Flu-like syndrome
4. Weight loss
5. Psychiatric symptoms (e.g. depression)
6. Headache
7. Fever
8. Loss of appetite
9. Unmasking of other diseases e.g. thyrotoxicosis

These complications are transient and are commonly treated by reassurance of the patient. In patients with absolute neutropenia one may need to use granulocyte stimulating drugs and rarely blood transfusion if haemoglobin is very low.

Drug Interactions in Co-infection with HIV

DDI and D4T plus interferon/ribavarin cause mitochondrial toxicity.

Recommendation: Avoid zidovudine with ribavarin. This is associated with higher anaemia rates. Avoid zidovudine when treating hepatitis C as well.

Some nucleosides and nucleotides are hepatotoxic, so regularly monitor with LFTs or completely avoid if there is decompensated liver failure.

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