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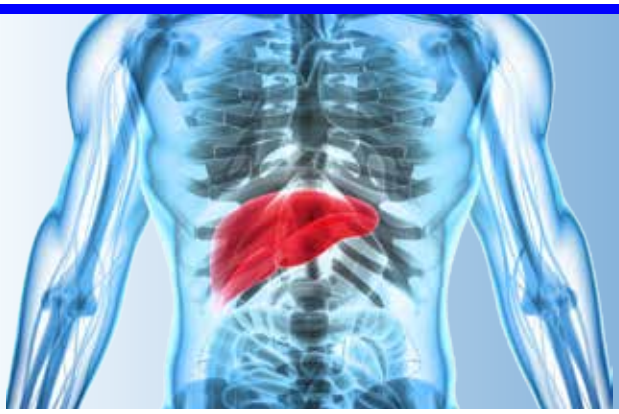

Viral Hepatitis

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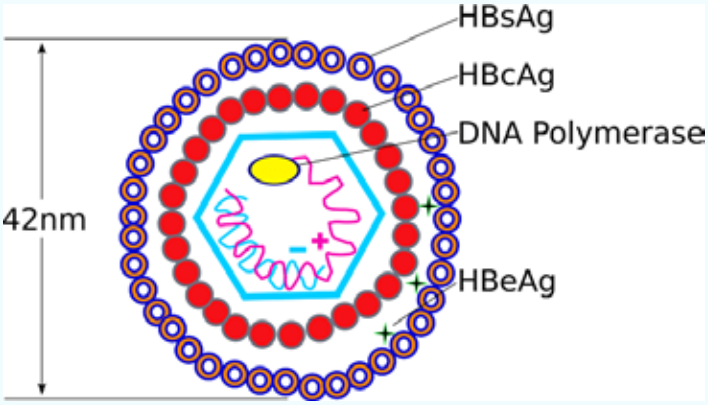
***Figure 1*: Structure of Hepatitis B virus (HBV)**



BACKGROUND

Hepatitis is the inflammation of the liver. There are various causes of hepatitis including viruses, bacteria, drugs, alcohol, and aflatoxins, of which viral causes are among the most common culprits.[1] Viral hepatitis is most commonly caused by different identified groups named alphabetically to include A, B, C, D and E. Hepatitis B and C have the most clinical significance[1] and hence this discussion focuses on the two, but mostly hepatitis B which is the most prevalent.

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus [2] (see figure 1) that infects the liver causing inflammation and hepatocellular damage. Hepatitis C virus on the other hand, is made-up of single-strand RNA and has six genotypes, numbered 1 to 6. There are also subtypes designated with a letter, for example, 1a or 1b. The genotypes determine which treatment one gets.[3]

EPIDEMIOLOGY

Hepatitis B virus is highly prevalent worldwide, with over two billion people exposed,[4] and an estimated 257 million living with the infection (defined as hepatitis B surface antigen positive). Majority of these live in sub-Saharan Africa and Southeast Asia.[1, 5] Globally, every year, fifty million new cases occur.4 By 2016, 71 million people were living with chronic hepatitis C (HCV) worldwide, and of these, 399,000 deaths occurred due to liver cirrhosis or hepatocellular carcinoma.[3, 6]

According to the Uganda Population-based HIV Impact Assessment survey (UPHIA), it is estimated that 4.1% of the population in Uganda aged 15-64 years has chronic hepatitis B infection. (See figure [2] below). The disease prevalence, however, varies from region to region, being highest in the north, and lowest in the southwest of the country at 4.6% and 0.8% respectively.[7] Studies on HCV prevalence in Uganda have shown inconsistent findings.[8, 9]

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Dear Reader,

Greetings and welcome to this quarter's ATIC newsletter.

As you all are aware, we are battling a major pandemic – COVID-19 – that has stretched many health systems across the world. With no cure yet, we hope that you continue to play your part in halting the spread of this disease. It's in your power to observe social distancing guidelines, ensure hand hygiene, cough and sneeze etiquette, and please and do wear your face mask correctly.

Now, back to this quarter's newsletter: Most of the questions that came from you, health workers, to the ATIC call centre revolved around hepatitis and so in this newsletter our team, led by Dr Eve Ahairwomugisha, delve into this condition.

We have answered your questions on the epidemiology of both hepatitis B and C. If you needed clarity on the treatment algorithm for this disease, we have you covered. How do you manage hepatitis in pregnant women and children? We've responded to all these with the facts. And yes, there's the ASK ATIC section too where we answer some of your questions that came through our ATIC toll-free line and WhatsApp platform.

Do you have any questions or comments about any of our services? Then get in touch. You can do so through our toll-free call centre number, **0800200055**, or WhatsApp: **+256787311883**. You can also email us: **training@idi.co.ug**

Stay safe!

Carolyne Amuge

Research and Communications Officer

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Figure 2: **Map of Uganda Showing Hepatitis B Prevalence by Region**

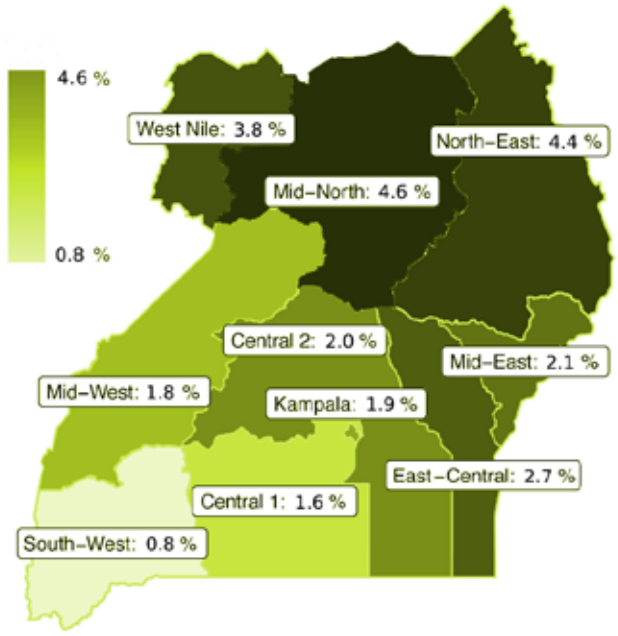
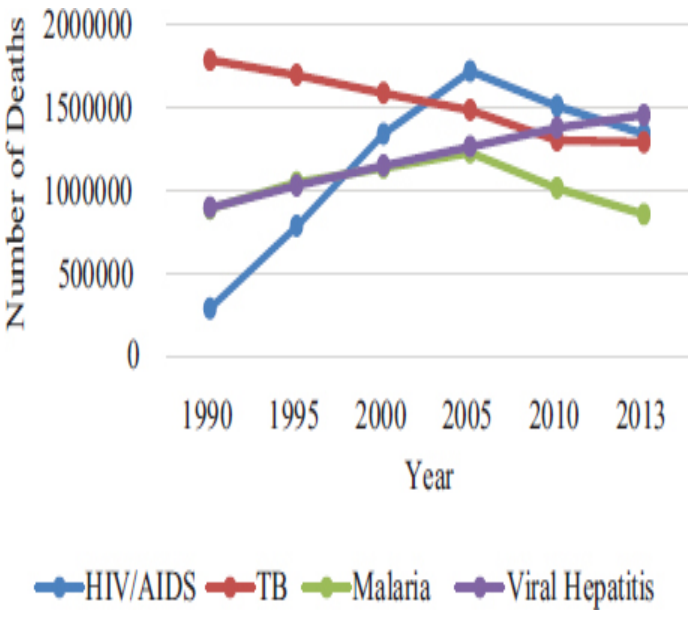


Figure 3**: Mortality associated with viral hepatitis in comparison with other infectious diseases.**



NATURAL HISTORY

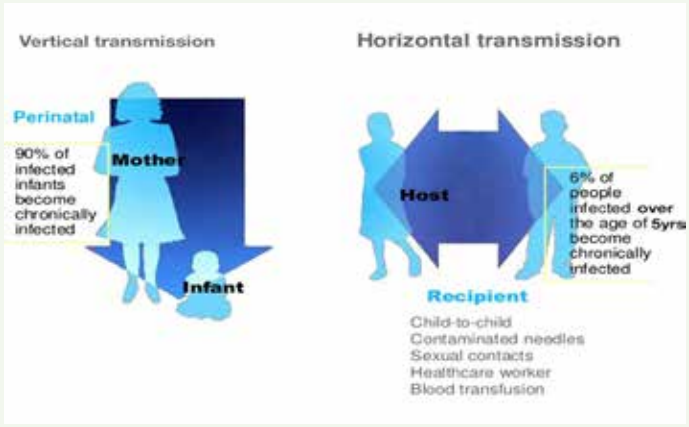
HBV and HCV infections cause both acute and chronic hepatitis. The HBV infection when acute, may or may not be symptomatic and usually resolves within six months. The symptoms for the acute infection may include fever, weakness, nausea, abdominal pain, headache, and yellowing of the eyes.[1]

HBV infection can be eliminated by natural immunity.[10] Infection acquired after five years of age can spontaneously be eliminated in over 90% of the infected individuals within six months. This rate drops to 30%-50% for infections acquired before five years of age.[11] Those that fail to eliminate the infection enter the chronic phase of the disease in which majority may remain asymptomatic,[12] with a few progressing to liver cirrhosis but remaining relatively stable (compensated). A small percentage may decompensate and suffer complications such as ascites, hepatic encephalopathy, hematemesis, malnutrition, kidney failure and liver cancer, which increase the risk of death.[4] These complications manifest years after the exposure to the HBV infection and occur in about 30% of those with chronic infection. Close to 70% of those infected have inactive disease and may not require treatment. Chronic hepatitis B presents with persistence of the hepatitis B surface antigen (HBsAg) for more than six months after the acute infection.[13, 14]

The HCV incident infection is associated with early symptoms in 20% of people and may spontaneously clear within six months in 15-45% of infected persons. The remaining 55-85% develop chronic infection. The risk of developing cirrhosis in HCV infection is between 15-30% after 20 years of infection. As with HBV infection, cirrhosis in HCV infection can be compensated or decompensated.[3]

Transmission of Hepatitis B: The transmission of HBV can be categorised as vertical or horizontal. Vertical transmission occurs from mother to child during and around child birth while horizontal transmission is through contact with contaminated blood, child-to-child contact, contaminated needles, and occasionally sexual contact.[15]

Figure 4: **Vertical and horizontal transmission of hepatitis**



Transmission of Hepatitis C

Transmission of HCV is mainly associated with unsafe injection-use practices and procedures, for example, surgical and dental care procedures. Other modes of transmission include mother-to-child transmission, percutaneous procedures like tattooing and body piercing, and infrequently, sexual transmission.[16, 17]

Misconceptions about Hepatitis B

There're some myths about HBV spreading through touching, coughing, sharing utensils, sharing beddings, sharing toilets, hand-shakes and sweat contact. This is not true. HBV does not spread through such ways but only when body fluids from an infected person enter another person through injection/needle pricks or blood transfusion.

CLINICAL PRESENTATION OF CHRONIC VIRAL HEPATITIS

Progression to cirrhosis is suspected when there is evidence of impaired hepatic synthetic function (hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia) and reduction in liver size. A patient with chronic viral hepatitis infection may present with features of advanced liver disease like portal hypertension, esophageal gastric varices, spontaneous bacterial peritonitis, hepatic encephalopathy and hepato-renal syndrome.[4] Physical examinations may be normal, or there may be stigmata of chronic liver disease such as spider angiomas (spider naevi) palmer erythema, splenomegaly and gynecomastia. Patients with decompensated liver cirrhosis may also have jaundice, ascites, peripheral edema, and encephalopathy.[14]

Figure 5: Jaundice (icterus) in Chronic Hepatitis Infection.

Figure 6: Ascites, varicose and Hepatocellular Carcinoma

***Fig.* 6a**: Ascites

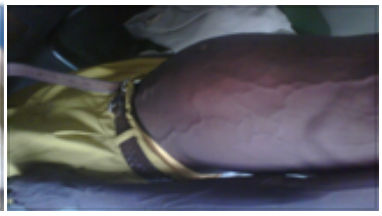


Fig 6b: Varicose veins

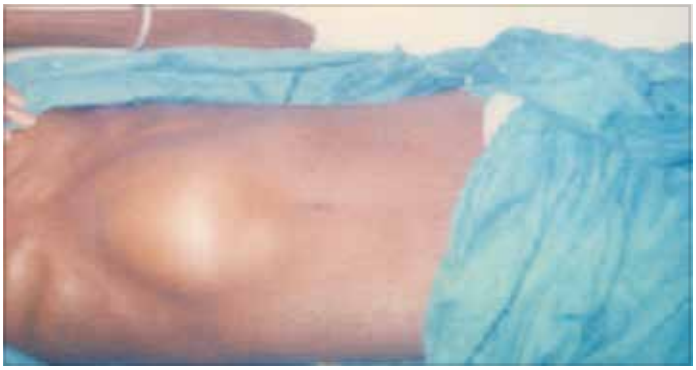
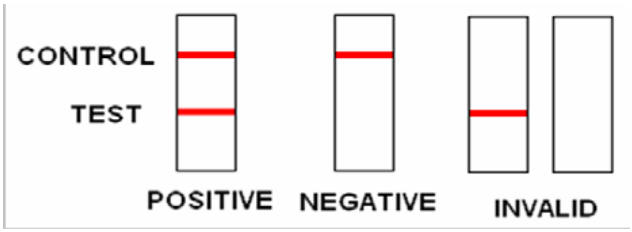


Fig 6c:Hepatocellular Carcinoma

Diagnosis of Hepatitis B

A Hepatitis B surface antigen (HBsAg) is the initial test to be carried out. A positive result means that one has HBV infection.[13] However, this test does not distinguish between chronic and acute infection.

Interpretation of the rapid HBsAg test is shown in figure 7 below



Diagnosis of Hepatitis C

A serological assay, antibody or antibody/antigen using a Rapid Diagnostic Test (RDT) is done to detect for a past or present infection in adults and children above 18 months. HCV-RNA must be done to confirm evidence of HCV virus.[3, 18] The preferred assay for evaluation of HCV infection early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months. However, infants should be at least two months old for this test to be reliable. [18]

Tests to be done on HBV-infected patients before deciding whether or not to treat:

A complete blood count and Liver Function Tests (LFTs) should be done to calculate APRI (AST-to-platelet ratio index), hepatitis B viral load and HIV test.

APRI = [(AST/ULN) X 100] / Platelet Count (10^9/L)

- AST is the patients test result in IU/L.
- ULN is the upper limit of normal for AST result got from the reference range of the laboratory where the liver test was done.
- APRI is the preferred available non-invasive test to assess for the presence of cirrhosis.
- An APRI score of >2 in adults indicates cirrhosis.[18]

Hepatitis C treatment eligibility criteria/who to treat:

The World Health Organization (WHO) recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age and older, irrespective of the disease stage.[3]

For hepatitis B, the following categories should be treated:

Category one: All children, adolescents and adults with CHB (HBsAg positive for six months and more) with clinical evidence of cirrhosis, and or adult patients with an APRI score > 2 should be treated regardless of the HBV viral load, HBeAg, ALT or HBeAg results.

Category two: Patients who are co-infected with HIV and HBV regardless of the viral load, CD4 count, WHO stage, liver enzymes or HBeAg status.

Category three:

- All patients without clinical evidence of cirrhosis with an APRI score of <2 but are 30 years and above.
- Persistent elevation of ALT (ALT at least two times above the upper limit of normal on three occasions done at least every three months over a period of 6-12 months).
- HBV viral load more than 20,000 IU/mL.
- All the above three conditions have to be met for the treatment decision.[12, 18]

Who should not be treated but monitored?

All patients who do not fall in the above three categories, an annual clinical assessment that includes a complete blood count, liver function, APRI score, abdominal ultrasound scan, HBV viral load and other routine tests like HIV should be done.[18]

Baseline Laboratory Investigation before Initiating HBV Anti-Viral Therapy

Renal function tests and a urinalysis should be done to rule out existing renal disease as the first line anti-retroviral used to treat HBV infection (Tenofovir disoproxil fumarate) causes renal toxicity.

An HBeAg may also be done where feasible. However, interpreting the results should be done cautiously as a positive test means active disease while a negative test may mean nothing because some patients with active disease and high viral load have a negative HBeAg test.[12]

Why treat for Hepatitis B & C infection?

The primary goal of treating HBV infection is to prevent progression to cirrhosis and hepatocellular carcinoma (HCC). This goal is achieved by using anti-viral drugs to suppress HBV viral load1 while the primary goal of antiviral drugs in HCV infection is sustained virological response (SVR).[19] If the blood tests are negative for the virus three months after completion of acute HCV treatment, then the patient is considered cured.[3, 18]

What to treat with:

Tenofovir disoproxil fumarate and Entecavir are the recommended antiviral drugs for HBV infection. Entecavir is recommended for children aged [2-11] years (who weigh at least 10 kg) and Tenofovir disoproxil fumarate in adolescents aged more than 12 years and adults weighing at least 30 kg. On the other hand, Tenofovir disoproxil fumarate + Lamuvidine + Efivarenz (TDF/3TC/EFV) or Tenofovir disoproxil fumarate + Lamivudine + Dolutegravir (TDF/3TC/DTG) is recommended for HIV/HBV co-infected patients.[12, 18] However, children who require treatment but do not meet the above categories should be managed by a specialist.

Regarding HCV, pan genotypic, directly acting antiviral agents (DAA) are recommended for persons aged 18 years and older.[3, 18]

Table 1: DAAs treatment for HCV patients without cirrhosis.

Glecaprevir/ Pibrentasvir	Sofosbuvir/ daclatasvir	Sofosbuvir/ Velpatasvir
Eight weeks (patients with genotype 3 and prior been treated with interferon or ribavirin, treat for 16 weeks)	12 weeks	12 weeks

Adapted from WHO hepatitis C guidelines, 2018.

CHC infected adult patients who have compensated cirrhosis should be treated with Sofosbuvir/ Velpatasvir for 12 weeks or Sofosbuvir/daclatasvir for 24 weeks.[18]

In adolescents aged 12-17 years of age or weighing 35 kg with CHC infection, MoH recommends sofosbuvir/ledipasvir for 12 weeks in genotypes 1,4,5,6; sofosbuvir/ribavirin for 12 weeks in genotype 2; sofosbuvir/ribavirin for 24 weeks in genotype [3.18]

In children who have CHC and are less than 12 years, the recommendation is that treatment is deferred until they are 12 years old.[18, 19]

Monitoring of patients on treatment

Review one month after initiating treatment and at three months to assess for adherence and side effects.

At six months, a urinalysis or a renal function test should be done to assess for drug toxicity. The following should be done annually to assess response to treatment:

HBV viral load, liver enzymes, HBeAg (for those who are HBeAg positive at the beginning) and Alfa-feta protein for HCC screening.[1, 12]

Routine screening for HCC with abdominal ultrasound and Alfa-feto protein testing is recommended every six months for persons with cirrhosis, regardless of age and other risk factors, family history of HCC, persons aged over 40 years and all persons at risk of HCC.

In conclusion, patients who test positive for HBV and HCV should never be treated without further assessment of the patient's other parameters.

When to Stop Treatment:

HBV infection has no cure. Treatment should be administered for a long time, and sometimes, for a lifetime to avoid reactivation of the infection especially where follow up is a challenge.[18]

Hepatitis B Prevention Through Vaccination

The most efficient way of preventing HBV infection is through vaccination. Vaccination is only beneficial if the individuals have never been exposed to this virus.[14, 20] In Uganda, the strategies for vaccination are routine vaccination of all infants, individuals in high-risk groups such as health care providers, HIV-infected persons, persons receiving dialysis. The other strategy is prevention of perinatal HBV transmission.[3, 18]

Perinatal HBV transmission can be prevented by identifying HBV-infected (i.e. HBsAg -positive) pregnant women that need to be put on antiretroviral therapy and providing hepatitis B immunoglobulin and three serial hepatitis B vaccine to their infants with the first vaccination dose given within 12 hours of birth.[21]

HEPATITIS B VIRUS AND PREGNANCY

Management of HBV infection in pregnancy is challenging.[22, 23] Acute HBV infection during pregnancy is usually mild and not associated with increased mortality or teratogenicity. MTCT of HBV can occur in utero, at birth and after birth. It is, therefore, important to have all pregnant mothers screened for HBV during the first antenatal visit.[24]

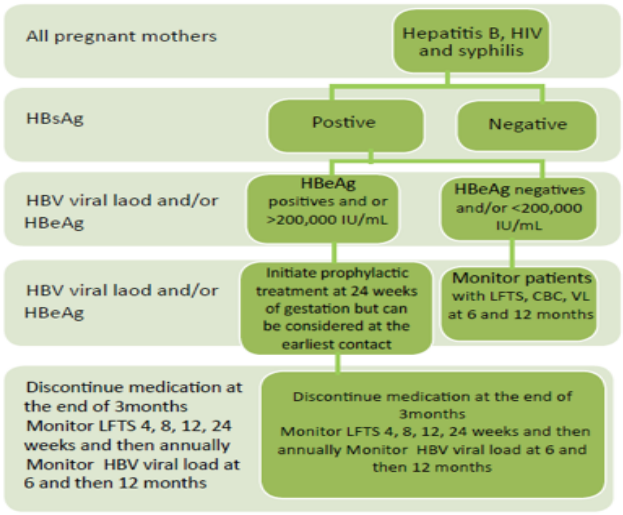
The risk MTCT of HBV despite proper prophylactic measures are a positive HBeAg, and/or a high maternal HBV DNA level.[21, 25]

The rate of transmission from mother to baby is at 10%. However, rates increase if the infection occurs at or near the time of delivery, with rates as high as 60%.[22,26] Research has indicated an increased risk of prematurity, low birth weight and antepartum hemorrhage as a result of CHB affecting pregnancy.[25]

Guidelines advise initiation of antivirals early at week 28 to allow sufficient time for viral load decline to less than 200,000 IU/mL, which appears to be safe and effective in lessening MTCT.[11] Please refer to the algorithm for HBV during pregnancy targeting PMTCT below.

The three antivirals that are considered safe in pregnancy are lamivudine (3TC), telbivudine (TBV), and Tenofovir disoproxil fumarate (TDF). TDF is the preferred agent for treating HBV in pregnancy given its high genetic barrier to resistance, favourable safety profile, and efficacy.[23, 27] TDF for MTCT should be stopped three months after delivery.[18]

Figure 8 Suggested Management of HBV in Pregnant Patients



Adapted from MoH18

Hepatitis B in Children

In highly endemic areas, HBV is most commonly spread from mother to child at birth (perinatal transmission) and through horizontal transmission (exposure to infected blood) occurring from an infected child to an uninfected child during the first five years of life. The development of chronic infection is very common in infants infected through their mothers or before five years of age.[25, 28]

Hepatitis B vaccine is the mainstay of prevention.[1,18] The Ministry of Health of Uganda incorporated HBV vaccination into the routine immunisation schedule for children. Three doses are recommended for routine vaccination. As per UNEPI guidelines Uganda, it is given at six weeks, 10 weeks, and at 14 weeks for children.[18]

In order to select children who should be treated with antiviral drugs, the ALT levels (reflecting liver damage), HBeAg status, serum HBV DNA levels (reflecting the viral-replication activity) and liver histology (reflecting disease progression) are evaluated.[20, 29]

As we note from this, it requires careful evaluation to determine children who will require treatment. Therefore, in Uganda, it is recommended that children who are hepatitis B positive should be referred to, evaluated and treated by a paediatrician.

If decompensated cirrhosis is absent, interferon-alpha is the first-line antiviral treatment. Nucleos(t)ide analogues (NAs), such as lamivudine, adefovir, entecavir and Tenofovir disoproxil fumarate are also available for the treatment of children, although the eligible age differs. If decompensated cirrhosis is present, NAs are the first-line antivirals.[29, 30]

Hepatitis C in Children

Children represent a small proportion of the hepatitis C virus (HCV) infected population. The natural course of CHC in children is not well understood.6, 31 However, a number of children have chronic HCV infection and are at risk of complications. MTCT is a known risk of infection, so children born to these women should be evaluated and tested for HCV. The rate of MTCT HCV infection is approximately 5% although rates are higher among women with inadequately controlled HIV coinfection, and women with higher HCV-RNA levels or viral loads (>6 log10 IU/mL).[31]

The rate of liver cirrhosis progression among children with CHC is slow and advanced liver disease is infrequent. However, some risk factors just as in adults like co-existing comorbid diseases, and those receiving hepatotoxic drugs should be monitored for disease progression. Once the diagnosis of CHC is made, the child should be monitored for disease progression.[30,32]

Children less than three years of age should not be treated except in special circumstances eg aggressive liver disease. Children who are ≥12 years old or weigh ≥35 kg with chronic HCV infection should be considered for treatment with DAAS options as in adults depending on the genotype.[14, 32]

ASK ATIC

1. Dear Doctor, I have a patient who has been getting hepatitis B vaccine and got late on his last dose for four months. Should I re-start the vaccination process?

ANSWER

The hepatitis B vaccine series should not be restarted when doses are delayed. Rather, the series should be continued from where it was left off even if it is delayed for a year. The vaccine recipient should receive the third dose.

2. Dear Doctor, I have a patient with a positive hepatitis B surface antigen and he is HIV negative, what should I do?

ANSWER

This patient should be assessed on whether he/she requires treatment or not and categorised as described in the text according to the treatment eligibility criteria:

- By examining him for obvious features of liver disease.
- Carrying out the following tests, a Complete Blood Count(CBC), platelet count, Liver Function Tests (LFTs): ALT (Alanine aminotransferase) and AST (Aspartate aminotransferase) and calculation of the APRI (AST-to-platelet ratio index), and HIV.
- Perform an abdominal ultrasound.

Patients who don't require treatment should be monitored annually as described in this newsletter..

3. Dear Doctor, I have a couple and one has tested hepatitis B positive while the other is negative. What should I do?

ANSWER

This couple should be counselled, starting with understanding what they know about hepatitis. Their fears should be alleviated by telling them the facts about the transmission of hepatitis B and the common myths as described in this newsletter. The positive spouse should be assessed on whether or not they require treatment while the negative one should be vaccinated.

4. Dear Doctor, I have a 9-year-old child HIV positive weighing 25kg on ABC/3TC/LPVr and suppressed but was recently found to be positive for hepatitis B surface antigen. What should I do?

ANSWER

Unlike in adults, the long-term effectiveness of antiviral treatment for chronic HBV (hepatitis B virus) infection in children has not yet been fully proven. The identification of children who need antiviral treatment is essential in the management of chronic HBV infection. Investigations that are needed to do this identification are costly and require skills that may not be readily available in your facility. These tests include ALT levels (reflecting liver damage), HBeAg status, serum HBV DNA levels (reflecting the viral-replication activity) and liver histology (reflecting disease progression). Liver cirrhosis due to chronic HBV infection should be immediately treated. This child should be referred to a centre with a specialist (paediatrician) for evaluation if they require treatment.

5. I have a couple that has brought their 6-year-old child to me. He was playing with a neighbour's child of the same age of which rumour has it that the neighbour's family has members known to be hepatitis B positive. The couple thinks their child could have acquired hepatitis B. The child is hepatitis B surface antigen negative. What should I do?

ANSWER

This couple seem to have a myth that hepatitis B is got through body contact. If the child was vaccinated against hepatitis B as per Uganda immunisation schedule, they should be counselled, highlighting the fact that hepatitis B is acquired mainly through infected blood and from mother-to-child. Establish that there was no blood contact during playing. Assure them that additionally, their child is already protected through vaccination according to the Ugandan Guidelines of Hepatitis B Routine Vaccination since 2002.

6. Dear Doctor, my patient was switched to TDF/3TC/DTG from TDF/3TC/EFV. She came two months back complaining of weakness, loss of weight and increased urinary frequency reporting that the symptoms started after the substitution. We diagnosed her with diabetes mellitus. How do we go about this situation?

ANSWER

There have been case reports where DTG has been associated with hyperglycaemia. There are currently no proper guidelines on this issue. However, from expert opinion, the patient should have the DTG substituted with EFV, given oral hypoglycaemic, and RBS monitored.

7. Dear Doctor, I have a patient who failed on first line TDF/3TC/EFV. He was started on AZT/3TC/ATV/r and developed severe anaemia that we think, after evaluation, is due to AZT. How should I manage this patient?

ANSWER

This patient having failed on first line, and not tolerating some drugs in second line means that his situation falls outside the common ART guidance in terms of next regimen. This patient falling outside the guidelines, can receive salvage regimen chosen after considering efficacy, drug-drug interaction and toxicity using expert opinion. In this case, Zidovudine can be replaced with Dolutegravir. Clinicians should also seek guidance and support from the centres of excellence.

8. Dear Doctor, I have a patient in my clinic who is on an implant for family planning and on TDF/3TC/EFV but she is pregnant. What could have happened?

ANSWER

ART drug interaction with some hormonal contraception has been documented with evidence that suggests that certain ARVs decrease the efficacy of some hormonal contraceptives in preventing pregnancy. Emerging evidence shows that efavirenz lowers the blood levels of certain progestins in up to 50% of women using implants. The Consolidated Guidelines for Prevention and Treatment of HIV in Uganda, 2018, recommend for an additional barrier method.

9. Dear Doctor, my patient is on implant and she gets intermenstrual bleeding. What should I give her? Should I remove the implant?

ANSWER

Before starting hormonal contraception, women should be advised on the expected bleeding patterns, both initially and in the longer term. For the implant, one of the most common side effects is spotting (light bleeding between periods). For every 10 women who use the implant, one will get it removed because of this irregular bleeding. Not everyone gets spotting, though, and for many women who get it, it goes away after a few months.

Take a clinical history to exclude sexually transmitted infections (STIs), check the cervical cancer screening history, and consider the need for a pregnancy test.

Combined oral contraceptives (COC) are given for up to three months continuously or in the usual cyclical manner. If any other infection is found, treat it as per the protocols.

10. Dear Doctor, I have a 9-year-old who has been weighing 24kg and I diagnosed her with pulmonary tuberculosis (PTB) and is currently on the continuation phase of anti TB RH paediatric dose - 4 tablets. On this visit she is now 25kgs. The guidance is we should give adult dose formulation; however, it starts at 33kgs. What should I do for this child?

ANSWER

As per national TB and leprosy guidelines, the child who is 25kg is supposed to take adult dosages and formulations yet the adult recommended dosage starts from 33kg.

So we need to calculate the dosage of this child kg per Bwt for each drug i.e. Rifampicin and Isoniazid. Rifampicin is given 10mg/kg/day while Isoniazid is given10 mg/kg/day.

This child needs 250mg of Rifampicin and 250mg of isoniazid.

The standard tablet RH formulation has 150mg R and 75 mg H. It is impossible to break the tablet into the desired right dose. So we can give this child 2 tablets of RH though it is a slightly high dose.

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