Hepatitis B is seen in children – how do we manage this?

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Hepatitis B in children

- Most HBV infections in children perinatal or early in life
- Hep B vaccine – South Africa 1995

- Mostly asymptomatic chronic hepatitis B infection – normal ALT, high viral load
- Most cases no treatment needed
- Chronic infection in 90% of neonates vertically infected vs 30% in <5 years old, <5% in older children

Current treatment options

- Older children and adolescents treatment options similar to adults
- Younger children – options are limited

Table 2 Antiviral drugs approved for children and adolescents with chronic hepatitis B virus infection[14]

	Ages approved for drug administration	Drug dosage	Drug formulations
Interferon alfa-2b	≥ 1 yr	6 million UI/m^2 three times a week	Subcutaneous injection
Peginterferon alfa-2a	≥ 3 yr	180 μg/1.73 m^2 once a week	Subcutaneous injection
Lamivudine	≥ 3 yr	3 mg/kg daily (maximum 100 mg)	Oral solution (5 mg/mL) or tablets (100 mg)
Entecavir	≥ 2 yr	10-30 kg: 0.015 mg/kg daily (maximum 0.5 mg)	Oral solution (0.05 mg/mL) or tablets (0.5 mg and 1 mg)
		> 30 kg: 0.5 mg daily	
Adefovir	≥ 12 yr	10 mg daily	Tablets (10 mg)
Tenofovir disoproxil fumarate	≥ 2 yr[1]	8 mg/kg daily (maximum 300 mg)	Oral powder (40 mg per 1 g) or tablets (150 mg, 200 mg, 250 mg and 300 mg)
	≥ 12 yr[1]	300 mg daily	
Tenofovir alafenamide	≥ 12 yr[2]	25 mg daily	Tablet (25 mg)

[1]Approved for ≥ 2 yr by the European Medicines Agency and ≥ 12 yr by the United States Food and Drug Administration.
[2]Approved independent of age for weight > 35 kg.

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Case 1

Case 1

- Child born to a mother who was known to have HIV, off ART during pregnancy
- Mother presented intoxicated with abruptio placentae on Christmas Day to local district hospital; unbooked and in preterm labour
- Baby delivered by emergency caesarean section at 31 weeks gestation, requiring resuscitation and respiratory support
- Commenced on AZT/3TC/NVP (standard neonatal antiretroviral therapy)
- Mother was restarted on firstline ART

Further course

- Mother's delivery HIV VL was 30,369 c/ml
- Baby's birth HIV PCR was indeterminate – according to current cut-offs, this would have been positive
- Repeat HIV PCR was again indeterminate
- Baby's ART was then switched to abacavir, lamivudine, lopinavir/ritonavir as per standard of care
- Both mother and baby recovered and the baby was discharged after a few weeks clinically well

- As all further HIV tests were negative and the initial HIV PCRs were indeterminate, antiretroviral therapy was stopped at 8 months of age

Clinically well…but

- The infant was clinically well and followed up, but incidentally had a raised ALT of 236U/l at age of 1 year
- Tested - hepatitis B surface antigen positive

  e antigen positive

  HBV viral load = log 8.5
- Mother's tested Hep BsAg positive years ago but this was missed (very far back in her results) – mother knew her HIV status, but not HBV status
- ?MTCT of HBV
- Transmission timing uncertain ?perinatal ?postnatal – reactivation after stopping ARVs (only 3TC)

- Child initially followed up at a research unit – virological testing to confirm truly HIV+ with small amount defective proviral DNA & no detectable viral load
- Normal renal function
- CD4 1258 (32%)
- HIV VL remained undetectable off ARVs
- ALT decreased a little, but remained elevated
- Followed initially - ?clearing HBV infection

Discussion

- Should we treat this child?
- Should we do a liver biopsy?
- If we need to treat this child – what medications?

  No suitable medications for small children with HIV and hepatitis B co-infection registered in South Africa to treat both

Advice

- Initial suggestion from colleagues with more experience of treating hepatitis B in children was not to treat, but to monitor

- However the ALT did not settle and she did not clear hepatitis B, remaining sAg and eAg positive
- We were uncertain regarding her HIV status as HIV ELISA, PCR and viral load remained persistently negative

- Eventually all agreed she needed treatment – ALT remained high
- We needed to treat both HBV and HIV

Management of Hepatitis B Virus Infection and Prevention of Hepatitis B Virus Reactivation in Children With Acquired Immunodeficiencies or Undergoing Immune Suppressive, Cytotoxic, or Biological Modifier Therapies

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Position. **We recommend that:**

1. **all HIV-positive children with HBV co-infection should start antiretroviral therapy irrespective of CD4 cell count;**
2. **HIV-HBV co-infected children should be treated with a tenofovir disoproxil fumarate or tenofovir alafenamide-based antiretroviral regimen.**

- 4 year old girl
- Clinically well – normal examination

- Weight 18kg Height 106cm BMI 16.2 (+0.64 SD)

- Liver stiffness was 4.9kPa = normal
- ALT running between 48-99 for over a year
- Hep B eAg remained positive, e Ab negative
- HBV Genotype A, no resistance mutations – viral load running log 8.2

Treatment

- Triple antiretroviral therapy active against both HIV and HBV
- Currently no such therapy available in South Africa for young children <10 years and <35kg

- Obtained donated TAF-FTC-Bictegravir
- Long process – approvals from PTC, provincial DOH, donating company, section 21 SAHPRA, importing courier company
- Started treatment in May 2023

- Child has remained clinically well
- ALT = 35 (down from 148 before starting Rx)
- HBV VL log 4.1 after 3-4 months of therapy (down from log 8.23)

Case 2

- 8 year old boy presented in fulminant liver failure
- Deeply jaundiced and comatose (stage 4 encephalopathy)
- INR 4.0 ammonia 176
- Supportive care was commenced to manage acute liver failure including admission to High Care
- Rapidly established that he would not be a candidate for liver transplant
- No reliable caregivers (both parents were regular substance abusers, maternal aunt was only working relative supporting entire extended family, child had been placed in his frail elderly greatgrandfather's care)
- No record of vaccinations

Past medical history

- Previously diagnosed with systemic juvenile idiopathic arthritis with macrophage activation syndrome

- Had been attending rheumatology service but was lost to follow up and off all medications for two years

- First 24 hours: hepatitis B sAg +
- Started lamivudine
- Core IgM positive, eAg +   HBV VL log 4.7

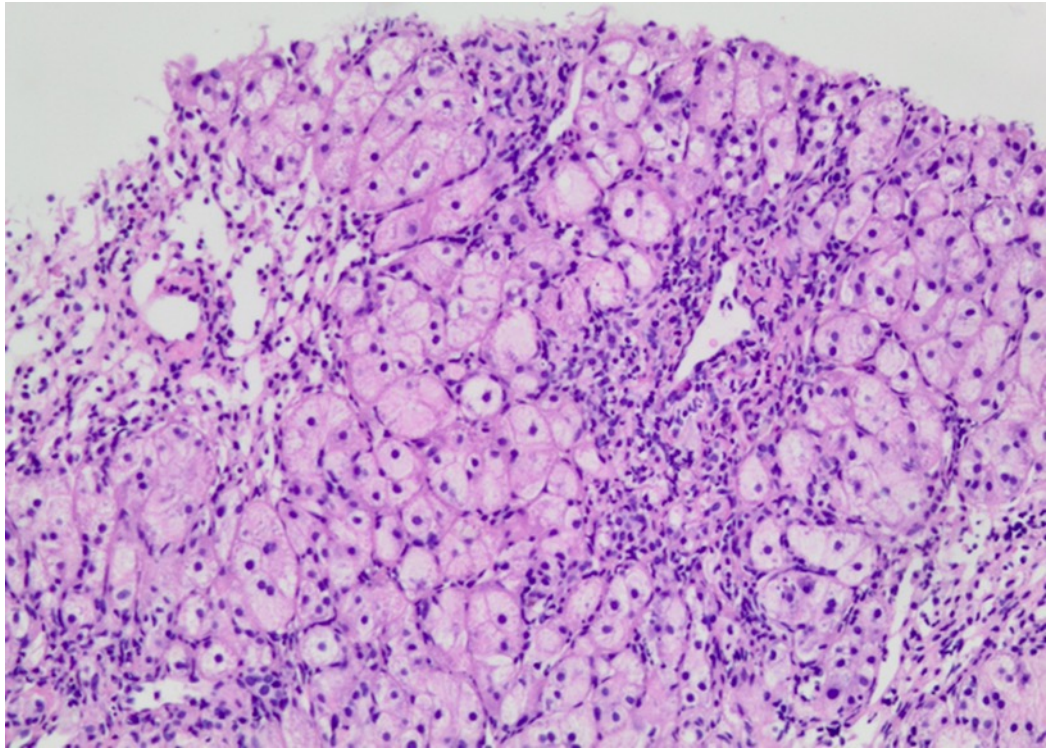
- After 48 hours: antismooth muscle antibody + (titre 1:40)
- Started prednisone for possible autoimmune hepatitis

- Actively managed cerebral oedema, neuroprotective measures
- Episodes of hypoglycaemia
- Supportive care

- After 2 weeks he started to improve, encephalopathy gradually resolved and he started walking around the ward complaining he was hungry

- Subsequently added tenofovir after discussion with Infectious Diseases colleagues – break an adult tablet and give part

Liver biopsy 2 months later



- Submassive necrosis with large areas of hepatocyte necrosis
- Portal tracts lymphocytes and plasma cells (interface hepatitis)
- Periportal fibrosis: Metavir stage F1
- No signs of viral inclusions
- Suggestive of autoimmune hepatitis

Discharge

- Now 9 years old - discharged into his aunt's care after prolonged stay at a children's home
- Significant difficulties attending hospital – adherent to therapy so far

- Confirmed both autoimmune hepatitis and hepatitis B infection
- Well with normal liver enzymes on low dose prednisone with azathioprine and combination tenofovir/emtricitabine (readily available at local clinic)
- Liver enzymes normal, HBV viral load undetectable

Case 3

Nephroblastoma due to start chemo

- 6yo boy referred to Tygerberg Hospital with a palpable abdominal mass arising from the right kidney
- Diagnosed with stage 3 nephroblastoma - planned for tumour resection and pre-operative chemotherapy

- Tested Hep B sAg positive before starting chemotherapy

Hepatitis B prophylaxis

- Hep B sAg+ eAg +   HBV VL log 8.5   ALT 25
- No need for hepatitis B treatment – risk of reactivation during chemotherapy

- No record of his vaccinations (previously noted missed doses)
- Mother had HIV and hepatitis B, he had tested HIV negative

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LAMIVUDINE FACILITATES OPTIMAL CHEMOTHERAPY IN HEPATITIS B VIRUS-INFECTED CHILDREN WITH HEMATOLOGICAL MALIGNANCIES: A Preliminary Report

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Subsequent course

- Started lamivudine 1 week before chemotherapy
- Had pre-op chemotherapy, right radical nephrectomy followed by post-operative chemotherapy
- Lamivudine given, but poor adherence in initial months

- ALT mildly elevated
- Hep B VL remained high
- Liver stiffness is 3.8kPa
- Genotype A – no resistance mutations detected
- Now a year later – completed chemotherapy and cured
- Starting him on tenofovir - breaking an adult tablet

3 scenarios where children with hepatitis B infection need treatment

1. HIV-HBV co-infection in young children

2. Acute liver failure needing ongoing treatment in young children

3. Chronic hepatitis B infection in young children needing immunosuppression or chemotherapy

Table 3 Differences among recommendations and indications for treatment of chronic hepatitis B virus infection in adults, adolescents, and children from five professional societies or international organizations

Organization	
ESPGHAN[16]	HBeAg-positive adolescents and children with persistent alanine aminotransferase elevation for at least 6 mo
	HBeAg-negative adolescents and children with persistent alanine aminotransferase elevation for at least 6 mo for at least 12 mo
	HBV DNA > 2000 IU/mL and either
	Moderate necroinflammation or fibrosis
	Mild inflammation or fibrosis with a family history of hepatocellular carcinoma
AASLD[17]	HBeAg-positive adolescents and children with both elevated alanine aminotransferase and measurable HBV DNA concentrations
	Therapy should be deferred when HBV DNA is < 10000 IU/mL, until spontaneous HBeAg seroconversion is excluded
APASL[18]	Non-cirrhotic HBeAg-positive adolescents and children when HBV DNA level is higher than 20000 IU/mL and alanine aminotransferase is more than twice the upper limit of normal for more than 12 mo
	Non-cirrhotic HBeAg-positive adolescents and children either HBV DNA > 20000 IU/mL and ALT more than two times ULN for more than 12 mo, or a family history of hepatocellular carcinoma or cirrhosis and moderate-to-severe inflammation or pronounced fibrosis
	Non-cirrhotic, HBeAg-positive chronic HBV infection, HBV DNA < 20000 IU/mL and moderate to severe inflammation or pronounced fibrosis
	Non-cirrhotic, HBeAg-negative chronic HBV infection, HBV DNA > 2000 IU/mL, and ALT more than two times ULNNon-cirrhotic, HBeAg-negative chronic HBV infection and moderate to severe inflammation or pronounced fibrosis, regardless of HBV DNA concentration
EASL[11]	A conservative approach is warranted

Current issues for children with hepatitis B

- Clinical approach based on expert opinion due to a lack of high quality data
- Lack of appropriate antiretroviral therapy for children <10 years with HIV-HBV co-infection
- Lack of paediatric formulations available
- Many medications not registered with SAHPRA for children and require section 21 approval


QUESTIONS