TRAIN-THE-TRAINER MANUAL

HBV CLINICAL MANAGEMENT

Supported through a restricted educational grant from Gilead Sciences.
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DISCLAIMER

Gilead Sciences played no role in the development of this manual. Additionally, the views expressed in this manual do not reflect those of the World Health Organization (WHO), whose normative guidance is cited at various points throughout the manual, unless otherwise explicitly stated through a citation.
The International Association of Providers of AIDS Care (IAPAC) established its African Regional Capacity-Building Hub with a mission to strengthen clinician capacity around HBV, HCV, and HIV clinical management. The Hub’s work is advanced in collaboration with national, regional, and international stakeholders, and through a restricted educational grant from Gilead Sciences.

The Hub is aligned to assist with ongoing efforts to expand access to the HBV, HCV, and HIV screening, testing, prevention, care, and treatment on the African continent. The Hub’s 2015-2020 goals include:

• Supporting countries to integrate World Health Organization (WHO), IAPAC, and other relevant normative guidance, including national guidelines, in relation to their HBV, HCV, and/or HIV responses;
• Increasing clinician capacity to implement HBV, HCV, and/or HIV normative guidance, along their respective continua, in specialized and primary care settings based on needs specifically determined at clinical sites; and
• Promoting continuing education and metrics-based certification as mechanisms to trigger continuing quality improvement, provide quality assurance, and address health workforce retention concerns.

IAPAC is the Hub’s Secretariat, and its association and academic partners for content development are the International Association for the Study of the Liver (IASL), the Makerere University College of Health Sciences (Kampala, Uganda), and the University of Cape Town’s Division of Hepatology (South Africa).
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<td>AASLD</td>
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<td>acute liver failure</td>
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<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>Anti-HBc (HBeAb)</td>
<td>hepatitis B core antibody</td>
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<tr>
<td>Anti-HBe (HBeAb)</td>
<td>hepatitis B e-antibody</td>
</tr>
<tr>
<td>Anti-HBs (HBsAb)</td>
<td>hepatitis B surface antibody</td>
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<td>APRI</td>
<td>aspartate aminotransferase to platelet ratio index</td>
</tr>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<tr>
<td>ARV</td>
<td>antiretroviral</td>
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<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CAR</td>
<td>Central African Republic</td>
</tr>
<tr>
<td>cccDNA</td>
<td>covalently closed circular DNA</td>
</tr>
<tr>
<td>CD4</td>
<td>cluster of differentiation 4</td>
</tr>
<tr>
<td>CHB</td>
<td>chronic hepatitis B</td>
</tr>
<tr>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>DILI</td>
<td>drug-induced liver injury</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>dsDNA</td>
<td>double-stranded DNA</td>
</tr>
<tr>
<td>DTP</td>
<td>diphtheria–tetanus–pertussis</td>
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<td>eAg</td>
<td>e-Antigen</td>
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<tr>
<td>EASL</td>
<td>European Association for the Study of the Liver</td>
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<tr>
<td>ER</td>
<td>endoplasmic Reticulum</td>
</tr>
<tr>
<td>FDC</td>
<td>fixed-dose combination</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>gGT</td>
<td>Gamma glutamyl transpeptidase</td>
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<td>HAV</td>
<td>hepatitis A Virus</td>
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<td>HBIG</td>
<td>hepatitis B immune globulin</td>
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<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
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<td>HBx Protein</td>
<td>hepatitis B virus X protein</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HDV</td>
<td>hepatitis D virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IAPAC</td>
<td>International Association of Providers of AIDS Care</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IgG core Ab</td>
<td>immunoglobulin G core antibody</td>
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<tr>
<td>IgM core Ab</td>
<td>immunoglobulin M core antibody</td>
</tr>
<tr>
<td>IRIS</td>
<td>immune reconstitution inflammatory syndrome</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income countries</td>
</tr>
<tr>
<td>MTCT</td>
<td>mother-to-child transmission</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger RNA</td>
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<tr>
<td>NAs</td>
<td>nucleos(t)ide analogues</td>
</tr>
<tr>
<td>NIT</td>
<td>non-invasive test</td>
</tr>
<tr>
<td>NMA</td>
<td>network meta-analysis</td>
</tr>
<tr>
<td>pegIFN</td>
<td>peginterferon</td>
</tr>
<tr>
<td>PLHIV</td>
<td>people living with HIV</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>sSA</td>
<td>sub-Saharan Africa</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir disoproxil fumarate</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

**Purpose**
The purpose of this manual is to provide trainers with guidance and tips for leading a training using the IAPAC African Regional Capacity-Building Hub's *HBV Clinical Management* curriculum.

**Training Package**
The *HBV Clinical Management* training package consists of:

- Train-the-Trainer Manual
- Presentation slides for each module
- Participant handouts (e.g., guidelines, case studies)

**Target Audience**
The target audiences for trainings using this manual and the *HBV Clinical Management* curriculum are physicians and nurses, as well as health educators from a variety of settings, including:

- Healthcare facilities and clinics
- Medical and nursing schools
- Community-based organizations
- Other facilities serving people living with or at risk for HBV
ADULT LEARNING

LEARNING CYCLE

Kolb’s experiential learning cycle has four phases: concrete experience which leads the learner to make observations and reflections based on their experiences. These observations and reflections then inform the conceptualizations and generalizations made by the learner on the subject matter. The conceptualizations and generalizations are then tested by learners using actual experimentation. New insights from experimentation form the basis of new concrete experience, thus making a full cycle.

In general teaching and learning aims at effective change in three domains:

1. Cognitive (knowledge) “Head”
2. Psychomotor (skills) “Hand”
3. Affective (attitudes) “Heart”

FIGURE 1. Kolb’s Experiential Learning Cycle

KNOWLEDGE RETENTION

In general, humans remember:

- 20% of what they hear,
- 40% of what they see, and
- 80% of what they discover by themselves.

Research shows that in general adults do not concentrate beyond 40 minutes hence the need to have a variety of experiential learning designs.

NOTES FOR TRAINERS

Keep all of this in mind as you prepare your training: adult participants need to hear, reflect, interact, and practice new knowledge and skills; long lectures are not the most helpful methods for teaching adults.

Good training helps participants discover what they already, and validates their own experiences and knowledge, as well as provides new information. Finding ways to train participants through a combination of lectures, plenary discussions, small group work, and individual reflection – maximizes learning potential for participants.

KEY STEPS IN TRAINING DESIGN

1) Context Analysis. An analysis of the organizational needs or other reasons the training is desired. Consider:

a. What are the needs of the participants that the training will address?
b. Why is the training program seen as the recommended solution to an information gap?
c. What is the history of the institution with regard to staff in-service training?
d. Who will decide when the training should happen?
2) **User Analysis.** This analysis seeks to determine:

- a. For whom is the training relevant?
- b. What is the participants’ level of existing knowledge on the core content?
- c. How much time are the participants (or their employers) able to make available for the training?
- d. What kind of expertise or competencies should the trainers possess?

3) **Content Analysis.** Analysis of material relevant to the training. We seek to answer:

- a. What knowledge or information is currently used on the job?
- b. What new knowledge, skills, or values are required to fill the information gap?
- c. What is the general learning style of the participants?
- d. What learning approaches and methodologies are suitable for the content and learning style of participants?

4) **Training Suitability Analysis.** Training is one of several solutions to service delivery gaps. Therefore we seek to answer:

- a. How will the training link to broader strategies for change?
- b. With whom should we share the draft curriculum for critical feedback?
- c. How will effective training result in a return of value to the organization that is greater than the initial investment to produce or administer the training?
- d. What materials and resource do we need to mobilize given budget provisions and limitations?

5) **Setting Objectives.** Although some trainers use teaching objectives that focus on what the trainer plans to do (teaching objective), it is recommended to use learning objectives in order to focus on the learner outcome.

An example of a teaching objective may be: “To update, reinforce, and provide new information regarding the clinical management of HBV.”

To modify this into a **learning objective**, start with the phrase: “At the conclusion of this activity, participants should be able to…” and then state the measurable activities the participants will be able to do, for example “describe the therapeutic options to reduce HBV-related morbidity and mortality.” Use specific action verbs (behavioral terms) to state cognitive outcomes:

<table>
<thead>
<tr>
<th>KNOWLEDGE</th>
<th>COMPREHENSION</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define</td>
<td>Explain</td>
<td>Apply</td>
</tr>
<tr>
<td>List</td>
<td>Express</td>
<td>Employ</td>
</tr>
<tr>
<td>Recognize</td>
<td>Describe</td>
<td>Demonstrate</td>
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<tr>
<td>Record</td>
<td>Discuss</td>
<td>Illustrate</td>
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<tr>
<td>Repeat</td>
<td>Identify</td>
<td>Interpret</td>
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<tr>
<td>State</td>
<td>Restate</td>
<td>Perform</td>
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<tr>
<td></td>
<td>Translate</td>
<td>Practice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use</td>
</tr>
</tbody>
</table>

6) **Monitoring and Evaluation.** We seek to answer:

- a. How will the training’s efficacy be evaluated during and after the training?
- b. How will we monitor and evaluate the manner the trainees have adopted or applied their learning?

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**NOTES FOR TRAINERS**

A few hours of thinking through all of the above listed questions will improve your ability to plan a training session that provides real benefit to individual participants, the group as a whole, and the community. Do not skip this important step!
WORKING DEFINITIONS

Training design: A complete and thorough description and “fleshing out” of the training that contains rationale, objectives, content/core topics, training methods, time, evaluation tools, facilitating roles and responsibilities, and materials and other resources needed.

Training: An educational process involving the creation and acquisition of knowledge, skills and attitudes.

Curriculum: A general description of the training or course that contains the:

- aim(s)/goal(s)/purpose
- specific objectives
- course content
- training methods/pedagogy
- timeframe for the training
- criteria for training evaluation

Syllabus: Contents of a course or training arranged according to a flow.

Module: A series of related activities responding to a particular set of objectives that can be undertaken independently; this may be one component of a curriculum.

NOTES FOR TRAINERS

A few final thoughts:

- It is important to always keep in mind your final goal: What is it you want the participants to have gained by the end of the training? What change in knowledge/attitudes/behavior do you want them to exhibit?
- Knowing how much to include in a training is a matter of experience. It is often useful to know the key items that you want to present, and make sure that there is time to address those items. Additionally, it is useful to have other topics for discussion or presentation prepared that may or may not be used depending on how quickly or slowly the group moves.
- Be ready to spend more time than you planned on key topics if it is clear the group needs more time to work through ideas or needs more time to practice; it is better to do a few things well than to speed through the entire curriculum and “lose” the group. If most of the group seems to understand and is ready to move on, but a few participants still seem confused or unsure, meet with them over breaks or after the training to spend more time with them to ensure that everyone understands the key concepts and skills.
- Be flexible to modify the training based on the group’s interest and learning priorities while keeping the end goal in sight. When the training diverges from the planned approach, assess whether the diversion is helpful in reaching the overall objective of the training. If it is just an interesting conversation but does not contribute to reaching the overall objective, suggest that it be moved to a lunch discussion.
DR TRAINING LOGISTICS

PLANNING AHEAD

**Administrative Support:** The course will need to be organized (advertise, receive registrations, find and book venue, etc.) and course materials will need to be prepared. This may take up to 10 days.

**Facilitator versus Co-Facilitators:** One facilitator is recommended per 60 in-service training participants for a one-day course. However, if the training agenda is split over two days held consecutively, it is recommended that two facilitators conduct the course.

**Training Venue:**

- You will require a room to hold up to 60 participants, with participants sitting in groups (preferably in groups of 5) around tables.
- You will require audiovisual equipment for use of PowerPoint presentation.
- You may print the slides onto overhead transparencies if you do not have PowerPoint projector capabilities.
- Organize payment for venues (if required).
- Familiarize yourself with the venue facilities (air-conditioning/heating, lighting, PowerPoint projector, tea and coffee facilities, toilets, parking, etc.).

**Geo-Mapping Trainings and Trainees:** We seek to geo-map the geographic reach of Hub trainings. We ask trainers to provide detailed updates after each training session regarding numbers of individuals trained accompanied by relevant non-identifying demographic information, including trainees’ academic credentials, practice settings, geographic locations (city/province), overall patient caseloads, and HBV-specific caseloads. Along with the date and location of the training session, the demographic information should be emailed to AfricanHub@iapac.org, with the subject line “HBV Trainees.”

**Costing:** Determine whether you need to pay for venue hire (especially computer facilities), catering, and printing. In some instances, such costs may be recouped by charging trainees an administrative fee.

**Publicity:** A draft promotional flyer has been supplied for you to modify. Sample text for email announcements will be provided.

**Registration:** You will need email or postal addresses of all participants in order to send pre-reading materials. Additionally, you may collect such information such as job title, contact details, and prior experience (and food preferences).

**Invoicing:** If participants are required to pay for the course, they will require an invoice for processing payment of the administrative fee.

**Catering:** It is recommended that morning coffee/tea, lunch, and afternoon coffee/tea are provided, in addition to water. You should check food preferences prior to placing a catering order.
ONCE REGISTRATIONS HAVE BEEN RECEIVED

Confirmations:

☐ Email participants to confirm their registration has been received and that they will receive pre-reading material at least 1 week (preferably 2 weeks) prior to the course.
☐ Organize name tags.
☐ Send all participants the pre-reading material at least 1 week (preferably 2 weeks prior to the course).
☐ Order a sufficient supply of training manuals (AfricanHub@iapac.org).

Printing Course Materials: This manual includes a series of handouts, including the training agenda, case studies, and self-assessment questions.

☐ Each document should be printed and collated by placing a colored piece of paper/divider at the end of each document to distinguish between documents.
☐ Do not forget to print out the evaluation form and course certificates (provided), too.

ON THE TRAINING DAY

You will require:

☐ All module slides.ppt
☐ Name tags
☐ Training agenda
☐ Training manuals
☐ Handouts (e.g., guidelines)
☐ Evaluation forms
☐ Certificates of completion
# TRAINING AGENDA

**IAPAC AFRICAN REGIONAL CAPACITY-BUILDING HUB: HBV IN-SERVICE TRAINING**

**NOTE:** Trainers may make adjustments to the training agenda, however it is recommended that all elements of the curriculum are covered by the conclusion of the in-service training.

<table>
<thead>
<tr>
<th>DATE:</th>
<th>FACILITY, CITY, COUNTRY:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM—9:00 AM</td>
<td>Registration/Check-In/Breakfast</td>
</tr>
<tr>
<td>9:00 AM—9:15 AM</td>
<td>Welcome, Introductions, and Training Overview</td>
</tr>
<tr>
<td>9:15 AM—9:45 AM</td>
<td>Module 1: Hepatitis B Virology</td>
</tr>
<tr>
<td>9:45 AM—10:15 AM</td>
<td>Module 2: Assessment of Liver Disease Stage</td>
</tr>
<tr>
<td>10:15 AM—11:00 AM</td>
<td>Module 3: First-Line Treatment of Chronic HBV</td>
</tr>
<tr>
<td>11:00 AM—11:30 AM</td>
<td>Break</td>
</tr>
<tr>
<td>11:30 AM—12:30 PM</td>
<td>Learning Activity: Case Study Application</td>
</tr>
<tr>
<td>12:30 PM—1:30 PM</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:30 PM—2:15 PM</td>
<td>Module 4: Identification and Management of HBV Treatment Failure</td>
</tr>
<tr>
<td>2:15 PM—2:45 PM</td>
<td>Module 5: HBV and Pregnancy Management Considerations</td>
</tr>
<tr>
<td>2:45 PM—3:15 PM</td>
<td>Module 6: Management Considerations for HIV/HBV Coinfection</td>
</tr>
<tr>
<td>3:15 PM—3:30 PM</td>
<td>Break</td>
</tr>
<tr>
<td>3:30 PM—4:30 PM</td>
<td>Learning Activity: Case Study Application</td>
</tr>
<tr>
<td>4:30 PM—5:00 PM</td>
<td>Summary and Evaluation</td>
</tr>
<tr>
<td>5:00 PM</td>
<td>Adjourn</td>
</tr>
</tbody>
</table>
Trainee Introduction

Time Required: Approximately 15 minutes

Instructions to Facilitator

1) Distribute course materials and name tags to participants.

2) Trainer introduction: Introduce yourself (and other facilitators if appropriate) and detail your background and experience. Alternatively, you may participate in the group introduction and icebreaker.

3) Participant introductions and icebreakers: There are many choices when it comes to icebreakers. You may have your own preferences.

4) Participants’ expectations: Ask the group to openly provide feedback on the four ‘G’s’:
   - Gives (what participants can give to the course)
   - Gains (what they hope to gain from the course)
   - Ghistlies (what they hope does not happen in the course (e.g., too simple, too advanced, not relevant, etc.)
   - Ground rules (what rules can the group agree upon (e.g., one person talk at a time, no single person to dominate discussion, etc.)

   You should write these down on butcher’s paper or on a whiteboard (or transparency) so you can regularly refer to them during the course and assess if the course is meeting their needs.

5) Discuss course objectives and outline of the one-day training agenda.

6) Address housekeeping issues – toilets, breaks, coffee/tea/water, or any other issues.
TRAINER GUIDE

Time Required:
Approximately 30 minutes

Learning Objectives:
1. Understand HBV characteristics
2. Describe the HBV replication cycle
3. Discuss HBV genotype distribution and impact
4. Explain the clinical significance of HBV genotypes and subgenotypes
5. Define the serologic and immunologic markers of HBV infection

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)
Hepatitis B Virus
- Enveloped partially dsDNA virus
- Member of the Hepadnaviridae family
- Found in blood and all body fluids
- 100 times more infectious than HIV
- Able to survive in dried blood for longer than 1 week

HBV Genome
- Enveloped partially dsDNA virus (42nm)
- Compact genomic structure (c. 3.2 kb)
- 4 overlapping open reading frames
- Reverse transcriptase/ DNA polymerase domain overlaps with surface gene
- Encodes 4 sets of viral proteins — HBsAg, HBcAg, viral polymerase and HBx protein

HBV Replication Cycle
1. HBV virions bind to the hepatocyte receptor — sodium taurocholate co-transporting polypeptide — and are internalized
2. In nucleus, genome replicated to form cccDNA
3. Translation of viral mRNA to proteins in cytoplasm
HBV Replication Cycle (continued)

4. Incorporation into ER and reverse transcription of RNA
5. Budding and secretion of viral cores to ER, and packaging in Golgi apparatus or
6. Recycling of genome to nucleus with replication of intranuclear cccDNA

Geographic Distribution: HBV Genotypes

HBV Genotypes in Africa
Impact of HBV Genotype on Disease Progression

Genotype C
- More frequently associated with severe liver disease and HCC than genotype B

Genotype
- Associated with seroconversion from HBeAg to anti-HBe at younger age than genotype C

Genotypes A and B
- Higher rates of antiviral response and HBeAg loss following pegIFN alfa than genotypes D and C

sSA: HBV Genotypes and Subgenotypes Clinical Outcomes

Genotypes A, D and E: Predominant hepatitis B genotypes in Africa
- Genotype A accounts for 90% of HBV infections in Southern, Eastern, and Central Africa
- Mean age of those infected with genotype A was 9.5 years younger than those with non-A
- predisposes to chronicity with an elevated risk of HCC
- Increased response rates to IFN

sSA: HBV Genotypes and Subgenotypes Clinical Outcomes (continued)

- Genotype D - reduced response rates to IFN; acute infection associated with increased risk of ALF
- Genotype E - West Africa
- Genotypes D, A, F and (in Asia) B - higher rates of HBeAg seroconversion
sSA: HBV Genotypes and Subgenotypes
Clinical Outcomes (continued)

HBV Sub-Genotypes in Africa
- South Africa (A,D): A1, A2, A3
- CAR (A,D,E): A1, D4
- Gambia, Nigeria, Congo, Rwanda, Cameroon (A): A4, A5, A6, A7
- Morocco (A,D): D1, D7, A2
- Egypt (D): D1
- Tunisia (D,F)

Clinical Outcomes
- Carriers with subgenotype A1 have lower HBV DNA than subgenotype A2 or genotype D
- Relative risk of HCC is 4 times higher with subgenotype A1 than non-A

HBV Genotypes: Clinical Outcomes
Genotypes B and C Common in Asia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genotypes B</th>
<th>Genotypes C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of HBeAg</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Spontaneous HBeAg clearance</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Histological activity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Rate of progression to cirrhosis</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Risk of hepatocellular carcinoma</td>
<td>Low (Japan, China) Variable (Europe) High</td>
<td></td>
</tr>
<tr>
<td>Response to interferon</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Response to nucleoside therapy</td>
<td>Better</td>
<td>Better</td>
</tr>
</tbody>
</table>

HBV Serologic Markers

HBsAg
- General infection marker
- First serologic marker to appear
- Infected considered chronic if persistent for > 6 months
- Indication of number of infected hepatocytes

HBeAg
- Indicates active replication of virus = high infectivity
- Nucleocapsid antigen
- Absent in precore or basal core promoter mutations
HBV Serologic Markers (continued)

- Anti-HBs (HBsAb)
  - Recovery and/or immunity to HBV
  - Detectable after immunity conferred by HBV vaccination

- Anti-HBe (HBeAb)
  - Generally indicates virus is no longer replicating
  - Present in HBsAg negative disease

- Anti-HBc total (HBeAb total)
  - Past exposure to HBV
  - Acute infection or reactivation

Immunologic Markers: Chronic HBV Infection

| Marker | Immune clearance | Immune escape | Immune tolerant | Immune tolerant B
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBVAb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBe</td>
<td></td>
<td>MEAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&lt;500000</td>
<td>&lt;500000</td>
<td>&lt;500000</td>
<td>&lt;500000</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>1</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Conclusions: HBV Virology

- HBV is a hepatotropic, oncogenic virus
- Sodium taurocholate co-transporting polypeptide is the newly identified hepatocyte receptor for HBV
- Replicative life cycle – co-cDNA is continually replenished and intercalated into the hepatocyte genome leading to chronicity
- Genotypes and subgenotypes determine risk of chronicity, hepatocellular carcinoma (HCC), and response to IFN therapy
MODULE 2

ASSESSMENT OF LIVER DISEASE STAGE & HBV TREATMENT CONSIDERATIONS

TRAINER GUIDE

Time Required:
Approximately 20 minutes

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)

Learning Objectives:
1. Understand the HBV spectrum of disease
2. Define phases of chronic HBV infection
3. Explain the assessment of liver disease stage
4. Describe HBV treatment considerations
REVEAL Study
Risk of HCC and Cirrhosis According to Baseline HBV DNA

Assessment of Liver Disease Stage
Liver Biopsy
- Liver biopsy has been considered the gold standard to grade and stage liver disease and assess the role of cofactors
- Standardised biopsy scoring systems - METAVIR and Knodell and Ishak scores

Not widely available in resource-limited settings
- Costly, invasive - risks of bleeding and pneumothorax
- Sampling error
- Expert histological interpretation

Assessment of Liver Disease Stage (continued)
Blood/Serum-based tests
- APRI
- Fib-4
- FibroTest (patented commercial test)
- Transient Elastography
- Fibroscan

Use of accurate and validated NAs in resource-limited settings
- Will help with optimal selection of persons with CHB for antiviral Rx
- Few validated studies in rSAA
Assessment of Liver Disease Stage (continued)

APRI and Fib-4
- Indirect markers of fibrosis (ALT, AST, platelets)
- Readily available in low- and middle-income countries
- Less costly
- No expertise required for interpretation
- Outpatient setting

Fibrotest
- Patented commercial test
- Expensive
- Accredited laboratory

NIDs not validated to assess all stages of fibrosis/cirrhosis

Assessment of Liver Disease Stage (continued)

APRI = (AST/ULN) x 100 / platelet count (10^9/L)
Validated for the diagnosis of both significant fibrosis ≥ F2 and cirrhosis (F4)
WHO Guidelines recommend the use of a single high cut-off ≥ 2 for identifying adults with cirrhosis (F4) and in need of antiviral therapy.

Fib-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L) x [ALT (IU/L)])
Validated for the diagnosis of significant fibrosis ≥ F3, but not cirrhosis

Assessment of Liver Disease Stage (continued)

APRI and Fib-4
- Optimal cut-off values that correlate with specific stages of liver fibrosis have been derived and validated
- Use two cut-off points for diagnosing specific fibrosis stages
  - Single cut-off would result in suboptimal sensitivity and specificity
- High cut-off with high specificity (fewer false-positive results) used to diagnose fibrosis ≥ F2
- Low cut-off with high sensitivity (fewer false-negative results) rules out the presence of particular stage of fibrosis
- Indeterminate values – follow-up and repeat testing
Assessment of Liver Disease Stage (continued)

- **Transient Elastography – Fibroscan**
  - Range is between 0 and 75 kPa
  - Less than 10 minutes to perform
  - Outpatient / community setting
  - Costly and requires operator training
  - Regular maintenance and recalibration

- **Lack of extensively validated cut-off values for specific stages of fibrosis**
  - Uses single cut-off value:
    - Significant fibrosis (F2) >7-8.5 kPa
    - Cirrhosis (F4) >11-14 kPa
  - Mean cut-off 12.5 kPa to diagnose cirrhosis

---

Assessment of Liver Disease Stage (continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Components</th>
<th>Classification</th>
<th>Requirements</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRI</td>
<td>ALT, AST</td>
<td>a=0.445, b=0.034</td>
<td>High volume and quality control</td>
<td>++</td>
</tr>
<tr>
<td>FibroScan</td>
<td>Ultrasound</td>
<td>n/a</td>
<td>Dedicated equipment</td>
<td>++</td>
</tr>
<tr>
<td>RIs-6</td>
<td>Asp A, ALT, albumin</td>
<td>n/a</td>
<td>n/a</td>
<td>++</td>
</tr>
<tr>
<td>FibroTest</td>
<td>Gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST)</td>
<td>n/a</td>
<td>n/a</td>
<td>++</td>
</tr>
</tbody>
</table>

---

Assessment of Liver Disease Stage (continued)

- Results of NTIs may be impacted by intercurrent diseases that may falsely increase or decrease the score:
  - Heavy alcohol intake (due to AST elevation from alcoholic hepatitis)
  - Use of drugs and traditional herbal medicines may increase ALT/AST
  - Malaria or HIV (may decrease platelet count)
  - Hepatitis fuses or acute hepatitis, congestive heart failure or a recent meal may also increase high liver stiffness (fibroscan)
2015 WHO Guidance on Assessing Liver Disease Stage

Fibrescan and APRI
- Most useful tests for assessing cirrhosis in LMICs (conditional recommendations)
- PPV for detection of cirrhosis was low for all HCs, in particular for APRI (detecting only 1/3 of persons with cirrhosis)
- Very limited evaluation in SSA

FIB-4
- Not considered or recommended
- Developed and validated for detection of fibrosis stages F3 and F4, not cirrhosis

Assessment of Liver Disease Stage & HBV Treatment Considerations

Current Treatment of Chronic Hepatitis B
- Chronic HBV infection: defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after an acute infection with HBV

Major advancements in therapeutic options – 2 major strategies
- Interferon (IFN)-based therapy
- Nucleos(t)ide analogue therapy

Assessment of Liver Disease Stage & HBV Treatment Considerations (continued)

Understanding the natural history and the phase of chronic infection
- Important in guiding treatment decisions

CURE is difficult as this is dependent on the eradication of hepatic intranuclear HBV cccDNA
Conclusions: Assessment of Liver Disease Stage

- PPV of all NTIs for the diagnosis of cirrhosis is low, especially for APRI.
- Many cases of cirrhosis will be missed using NTIs alone.
- Important to combine NTIs together with clinical criteria and other lab criteria (ALT and HBV DNA levels) to identify those in need of treatment.
- APRI is the WHO preferred NT to assess fibrosis.
  - Blood tests needed to calculate APRI score are routinely available at most health-care facilities, even in LAMCs.
  - No evaluation of APRI in people from sub-Saharan Africa.
- WHO: APRI single high cut-off >2 for identifying adults with cirrhosis (P4) and in need of antiviral therapy.
MODULE 3
FIRST-LINE TREATMENT OF CHRONIC HBV

TRAINER GUIDE

Time Required:
Approximately 45 minutes

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)

Learning Objectives:
1. Explain the goals of HBV treatment
2. Describe HBV treatment strategies
3. Identify approved therapies for HBV infection
4. Discuss the efficacy of HBV therapies
5. Define WHO-recommended HBV therapy
6. Understand how to monitor HBV therapy

Learning Objectives
- Explain goals of HBV treatment
- Describe HBV treatment strategies
- Identify approved therapies for HBV
- Discuss efficacy of HBV therapies
- Define WHO-recommended HBV therapy
- Understand how to monitor HBV therapy
Goals of HBV Treatment

Prevention of long-term complications of chronic hepatitis B
- Cirrhosis
- Liver failure
- Hepatocellular carcinoma

Goals of HBV Treatment (continued)

Difficult to measure these clinical outcomes – surrogate measures
- Biochemical: normalization of serum ALT
- Virological
  - Durable suppression to undetectable HBV DNA
  - Durable HBeAg loss or seroconversion to anti-HBe
  - Durable HBeAg loss seroconversion: to anti-HBs status
- Histological
  - Decrease in necro-inflammatory score
  - Possibly regression of fibrosis on liver biopsy

Goals of HBV Treatment (continued)

HBeAg clearance is the ideal endpoint of therapy
- Aim to reduce number of infected hepatocytes & reduce HBV viral replication level
- HBeAg serum levels reflect the transcriptionally active cccDNA
- HBeAg serum levels lowest in immune control phase
- HBeAg clearance is associated with:
  - Reduced incidence of cirrhosis
  - Reduced incidence of HCC
  - Improved survival
Goals of HBV Treatment (continued)

CURE IS DEPENDENT ON ERADICATION OF cccDNA

HBsAg clearance is the closest to cure in chronic HBV

Treatment Strategies for Chronic HBV

Interferon (IFN)-based therapy
- Dual Antiviral and immunomodulatory activity
- Finite course of treatment
- Aim for sustained off-treatment immune control
- Negative HBsAg, HBsAb, and HBV DNA <2,000 IU/ml through dual modes of action
- Successful in 30-50% patients

Nucleos(t)ide analogue therapy
- Antiviral activity
- Long-term (potentially indefinite) treatment
- Aim for on-treatment viral suppression (HBV DNA ≤)
- Maintained through continuous antiviral therapy
- Suppression of replication to undetectable levels to avoid resistance

Approved Therapeutic Options for HBV

- Standard Interferon
- Pegylated interferon
- Lamivudine
- Telbivudine
- Entecavir
- Tenofovir + emtricitabine

Sub-Saharan Africa
- Lamivudine and tenofovir widely available as part of HIV antiretroviral therapy
- Not always accessible for Rx of HBV monotherapy
- Entecavir not widely available, no generics
% BeAg Negative Chronic HBV

Factors Favoring IFN as Initial Therapy

- Favorable predictors of response
  - Genotype A or B = C or D
  - Low HBV DNA
    - Baseline: <10^5 copies/mL
    - 12 weeks: <20,000 copies/mL
  - High ALT (baseline) >2 x ULN
  - High activity scores on biopsy (A2)
- Specific patient demographics
  - Younger individuals
  - Young woman wanting future pregnancy

- Patient preference
- No coinfecion with HIV
- Concomitant HCV or HDV infection
Factors Associated with Choosing Nucleos(t)ides as Initial Therapy

- Favourable predictors of response
  - High ALT
  - Low HBV DNA (baseline < 1x10^7 IU/mL and on treatment)
- Specific patient demographics
  - Older people
- Patient preference
- Concomitant HIV infection
- No HCV coinfection
- Cirrhosis

HBV Treatment Strategies

What is the best HBV treatment in our setting?
- Interferon (IFN)-based therapy has best chance of HBsAg eradication with few Rx

BUT Interferon (IFN) has limitations in sub-Saharan Africa:
- Long immune tolerant phase
- High HBV DNA levels and often minimal necro-inflammation
- Liver biopsy assessment is advisable
- Expensive and close monitoring required

Majority of HBeAg negative in sub-Saharan Africa not suitable for IFN-based Rx
2015 WHO HBV Guidelines recommend entecavir and tenofovir as first-line Rx

Efficacy: Tenofovir and Entecavir

Network meta-analysis
- 21 pairwise comparison RCTs comprising 9073 HBsAg positive nucleoside-naive persons
- 15 trials comprising 2934 HBsAg negative nucleoside-naive persons

Tenofovir monotherapy had highest probability of achieving undetectable HBV DNA at end of 1 year of Rx
- HBsAg positive: 91.9% (95% CI: 74.7-98.9%)
- HBsAg negative: 97.6% (95% CI: 96.7-99.8%)

2015 WHO Guidelines for the Prevention, Care and Treatment of Hepatitis B Virus Infection
Efficacy: Tenofovir and Entecavir (continued)

Entecavir monotherapy: Undetectable HBV DNA at end of 1 year of Rx

- HBsAg-positive 64.5% (95% CI: 49.1–80.9%)
- HBsAg-negative 91.9% (95% CI: 87.3–95.1%)

All other antiviral therapies had very low probability of achieving this outcome

Long-Term Effectiveness of Entecavir and Tenofovir after 3 and 5 Years

Low cumulative rates of:

- Mortality
  - Entecavir: 3% and 3.0%
  - Tenofovir: 0.7% and 1.4%
- HCC
  - Entecavir: 2.9% and 8.6%
  - Tenofovir: 1.4% and 2.4%
- Genotypic resistance
  - Entecavir at 5 years of Rx (0.8–1.2%)
  - Tenofovir: no resistance at 8 years

Recommended NAs and Dosages for Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Tenofovir plus emtricitabine</td>
<td>Tenofovir 245 mg, emtricitabine 200 mg</td>
</tr>
<tr>
<td>Tenofovir (adult with compensated liver disease) and lamivudine:</td>
<td>65 mg once daily</td>
</tr>
<tr>
<td>Tenofovir (adult with decompensated liver disease)</td>
<td>1 mg once daily</td>
</tr>
</tbody>
</table>

*Tenofovir disoproxil fumarate (TDF) 245 mg is equivalent to tenofovir 135 mg and lamivudine 100 mg.
*Nucifor lamivudine fumarate (NLF) is an oral lamivudine prodrug that is biotransformed to lamivudine (lamivudine monophosphate).
**Recommended NAs and Dosages for Children**

<table>
<thead>
<tr>
<th>Childs weight (kg)</th>
<th>Treatment name</th>
<th>Recommended dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 10</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>11 to 20</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>21 to 30</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>31 to 40</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>41 to 50</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>&gt;50</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

*Childs with body weight < 20 kg should receive 10 mg x 4 weeks or 20 mg x 2 weeks.*

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**Assessment Prior to Treatment Initiation**

- Assess severity of chronic liver disease
- Assess viral load of viral replication
- HBV DNA, HBsAg and anti-HBc status (if available)
- Assessment for the presence of co-morbidities
- Lifestyle counseling
- Preventive measures
- HBsAg screening with HBV vaccination of non-immune family members and sexual contacts

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**Preparation for HBV Treatment**

- Patient counseling
  - Indications for treatment
  - Benefits and side-effects of treatment
  - Need for and willingness to commit to long-term treatment
  - Need for follow-up monitoring both on and off therapy
- Importance of full adherence for treatment
  - Efficacy of treatment
  - Risks of non-adherence
  - Risk of drug resistance
  - Progression of disease
  - Risk of acute liver failure with abrupt cessation of treatment
  - Cost implications of treatment and follow up
Toxicity of NAs
Nephrotoxicity: Assess renal function before NA initiation
- Serum creatinine level
- Estimated glomerular filtration rate
- Urine dipsticks for proteinuria and glycosuria

Toxicity of NAs (continued)
- Risk factors for renal dysfunction
  - decompensated cirrhosis
  - GFR <60 mL/min
  - poorly controlled hypertension and diabetes
  - proteinuria, active glomerulonephritis
  - solid organ transplantation
  - older age, BMI <18.5 kg/m2 or body weight <50 kg
  - boosted protease inhibitor for HIV
  - concurrent nephrotoxic drugs
  - Monitoring should be more frequent in those at higher risk of renal dysfunction

Toxicity of NAs (continued)
Nephrotoxicity: Assess renal function before NA initiation
- solid organ transplantation
- older age, BMI <18.5 kg/m2 or body weight <50 kg
- boosted protease inhibitor for HIV
- concurrent nephrotoxic drugs
  - Monitoring should be more frequent in those at higher risk of renal dysfunction
Monitoring Long-Term NA Therapy

- HBV DNA every 6-12 months
- HBsAg and HBeAg every 6-12 months
- ALT and AST (for APRI) annually
- Renal function (annually)
  - more frequently if risk factors for renal dysfunction
- Adherence to therapy
- Monitor for HCC
  - alpha-fetoprotein and ultrasound liver every 6-12 months

Stopping NA Therapy

CIRRHOSIS
- Lifelong NA therapy
- NO CIRRHOSIS
- HBeAg positive chronic HBV
  Consider stopping treatment if:
  - HBsAg loss and seroconversion to anti-HBe after completion of at least one additional year of treatment
  - persistently normal ALT
  - persistently undetectable HBV DNA
- Need close monitoring after treatment cessation (20W may relapse)

Stopping NA Therapy (continued)

NO CIRRHOSIS
- HBeAg negative chronic HBV
  - Lifelong NA therapy

Most patients with chronic HBV in sub-Saharan Africa will need lifelong therapy
Conclusions: First-Line HBV Treatment

- **CURE** is dependent on the eradication of intranuclear HBV cccDNA
- HBsAg clearance is the closest to cure in chronic HBV
- Tenofovir, entecavir, and peginterferon are preferred first-line drugs
  - Third generation NAs have high efficacy, very low rates of resistance & excellent safety record, but therapy is potentially lifelong
  - PEG-IFN offers finite therapy & chance for cure through dual antiviral and immunomodulatory action
- Majority of treatment candidates in sub-Saharan Africa are not suitable for IFN-based treatment

Conclusions: First-Line HBV Treatment (continued)

- 2015 WHO HBV Guidelines recommend tenofovir and entecavir
- Tenofovir has excellent resistance profile and 10% HBsAg seroconversion at 8 years
- Sustainable access to affordable generic NAs essential in sub-Saharan Africa, including for HBV monoinfection
MODULE 4
IDENTIFICATION AND MANAGEMENT OF HBV TREATMENT FAILURE

TRAINER GUIDE

Time Required:
Approximately 45 minutes

Learning Objectives:
1. Define primary and secondary HBV treatment failure
2. Understand the causes of and how to recognize HBV drug resistance
3. Explain how to monitor HBV treatment adherence
4. Describe the management of HBV treatment failure

Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)

Learning Objectives
- Define primary and secondary HBV treatment failure
- Understand the causes of and how to recognize HBV drug resistance
- Explain how to monitor HBV treatment adherence
- Describe the management of HBV treatment failure
Identifying HBV Treatment Failure

HBV TREATMENT FAILURE MAY BE PRIMARY OR SECONDARY

In settings with access to HBV DNA testing:

Primary antiviral therapy failure
- Failure of drug to reduce HBV DNA levels by ≥1 x log_{10} IU/mL within 3 months following initiation of therapy
- Rare in persons initiating and adhering to entecavir or tenofovir Rx
- Can occur in persons treated with lamivudine, adefovir or telbivudine

Secondary antiviral treatment failure
- Rebound of HBV DNA levels of ≥1 x log_{10} IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x log_{10} IU/mL decrease in serum HBV DNA)

In settings without access to HBV DNA testing:

Treatment failure and drug resistance suspected
- Use of antiviral drugs with a low barrier to resistance
  - documented or suspected poor adherence
- Rising transaminases
- Evidence of progressive liver disease
  - Elevation in ALT level tends to occur late, relatively poor predictive marker of resistance
Identifying HBV Treatment Failure (continued)

Confirmation of antiviral drug failure

- Sequencing the HBV DNA polymerase
- Identifying specific genetic markers of antiviral drug resistance

Identifying HBV Treatment Failure (continued)

Drug resistance

- Concerns with long-term NA therapy
  - Selection of drug resistant mutations
- HBV has high rate of replication with $10^{10}$ mutations generated daily
- Higher rates of NA resistance in individuals
  - High baseline HBV DNA levels
  - Longer duration of treatment
  - Slower treatment decline in HBV DNA levels
- Several drug resistance mutations in HBV polymerase
  - Cross-resistance to several NAs - limits future Rx options

Identifying HBV Treatment Failure (continued)

Drug Resistance

- Increased risk of multidrug-resistant hepatitis B, if treated sequentially with NAs with a low barrier to resistance (lamivudine, adefovir and tenofovir) as monotherapy
- Widespread use of lamivudine for persons with CHB and high HBV DNA levels in some countries has led to a high burden of lamivudine-resistant hepatitis B
Emergence of Drug Resistance

Emergence of Drug resistance
- Viral rebound with increasing HBV DNA levels
- Followed by biochemical breakthrough with rise in ALT
- Hepatitis flare and potential clinical decompensation

Approved NAs: HBV Treatment

- Lamivudine
- Emtricitabine
- Tenofovir
- Entecavir
- Adefovir
- Telbivudine

- Generic formulations of lamivudine/emtricitabine & tenofovir available in sub-Saharan Africa as part of ART at significantly reduced prices
  - not always available for Rx of HBV reinfection
- Generic entecavir preparations are not available in sub-Saharan Africa
- Globally, both originator and generic entecavir prices are significantly higher than for lamivudine and tenofovir

Cumulative Rates of Resistance with Oral Agents in Nucleos(t)ide-Naive Patients

Due to insufficient data, different patient populations and methodological differences

- Lamivudine
- Emtricitabine
- Tenofovir
- Entecavir
- Adefovir
- Telbivudine
Preventing HBV Treatment Failure

Adherence
- Treatment adherence is essential for HBV viral suppression
- Adherence should be reinforced in all individuals with confirmed or suspected antiviral resistance
- Adherence is dependent on a number of factors:
  - Patient's insight into need for treatment and risks of non-adherence
  - Guaranteed secure supply of medication
  - Transport to healthcare centre supplying antivirals

Monitoring Adherence to HBV Antiviral Therapy

Counselling
- Pre- and post-initiation of treatment essential to ensure adherence
- Monitoring of adherence is essential
- Self-reporting of missed doses by patient or caregiver is unreliable
- Pharmacy refill records:
  - Obtaining pharmacy refill at irregular intervals
  - Overestimate adherence on sole basis of pharmacy refill records
  - Collecting medications does not equate with adherence
- HBV DNA Viral load monitoring:
  - Optimal way to diagnose and confirm treatment failure

Management of HBV Treatment Failure

Network meta-analysis: HBsAg positive patients
- Seven RCTs of antiviral comparisons based on HBsAg or HBeAg+ data were included for outcomes of undetectable HBV DNA (<200 copies/mL) or 60 IU/mL
- Six studies (771 persons) for the outcome of HBsAg seroconversion
- Treatments evaluated in HBsAg+ positive pts:
  - Option to reduce level of efficacy
  - Continuation without add-on therapy
- Included the following agents:
  - Tenofovir, emtricitabine, lamivudine
  - Tenofovir and emtricitabine (in combination with tenofovir)
Management of HBV Treatment Failure (continued)

Network meta-analysis: Treatments evaluated in HBeAg positive patients – tenofovir followed by entecavir + adefovir combination therapy had highest probability of achieving:
- Undetectable HBV DNA (66.7% and 33.9%, respectively)
- HBeAg seroconversion (39.8% and 31.2%, respectively) at the end of 1 year of treatment among all the unselected treatments.

After 1 year of tenofovir treatment:
- 86% (95% CI 81.8-89.2%) of lamivudine-resistant patients would be expected to achieve undetectable HBV DNA.
- 17.5% (95% CI 14.4-20.6%) HBeAg seroconversion.

No RRA was conducted for lamivudine-resistant HBeAg-negative persons.

Management of Lamivudine Resistance

2015 WHO Guidelines recommend switch to tenofovir monotherapy (HBeAg+ patients):
- Highest probability of 1 year of achieving undetectable HBV DNA levels
- Continuing ineffective antiviral therapy with ongoing HBV replication
  - Increased risk of disease progression to cirrhosis and HCC
- Use of tenofovir, which does not share cross-resistance with other NAs
  - Sensitivity selection of better: compensatory mutations and development of drug resistance, with reservoirs of resistant HBV variants.

Management of Lamivudine Resistance (continued)

- Lamivudine resistance (L180M + M204V) confers cross-resistance to telbivudine and entecavir, but not tenofovir
- Entecavir resistance is more LAM-resistant CHB with adefovir or telbivudine or entecavir
  - Leads to the selection of multidrug-resistant hepatitis B
Conclusions: Identification and Management of HBV Treatment Failure

Consider Treatment Failure
- Rising ALT
- Progression of liver disease

Assess Adherence
- Especially with clinical deterioration and virological failure on therapy
- Exclude other causes of clinical deterioration
  - DU
  - Other viral infections
  - Development of HCC

Conclusions: Identification and Management of HBV Treatment Failure (continued)

Management of Resistance
- First-line nucleoside
  - Highest probability of achieving or maintaining undetectable HBV DNA levels in persons with lamivudine-resistant HBV
  - Little evidence of advantage from the systematic review that adding NAs or combined use of NAs confers benefit in lamivudine resistance
  - TDF shows no cross-resistance avoids selection if further compensatory mutations and development of drug resistance, with reservoir of resistant HBV mutations
  - Simplifies clinical management and drug procurement in persons who have developed resistance to lamivudine, adefovir, entecavir, or telbivudine

...
TIME REQUIRED:
Approximately 30 minutes

LEARNING OBJECTIVES:
1. Explain the natural history of HBV in pregnancy
2. Describe HBV testing in pregnant women
3. Understand the treatment of HBV in pregnancy
4. Discuss prevention of mother-to-child transmission of HBV
5. Define how to recognize and address post-partum HBV flares

SUPPORTING MATERIALS:
- PowerPoint Slides
- Case Study (refer to Learning Activities section)
HBV and Pregnancy
Natural History and Pregnancy Outcomes

- Conflicting data on natural history
  - No worsening of liver disease in most women
  - Some reports suggest HBV reactivation, hepatic exacerbations
  - and fulminant liver failure may occur

Adverse pregnancy outcomes – some reports of higher rates of:
- Premature birth
- Gestational diabetes
- Anepistemic hemorrhage
- HBsAg-positive mothers need close follow up during pregnancy

Hepatitis B Screening in Pregnancy

HBsAg screening of pregnant women essential: AASLD and EASL
- First trimester of each pregnancy
- Pregnant women not immune to HBV and with risk factors for infection should be vaccinated against HBV – SAFE IN PREGNANCY
- Ongoing high-risk behavior during pregnancy and HBsAg status unknown
  - Test for HBsAg at admission for delivery
  - HBsAg-positive women should be referred for additional testing, counseling and medical management.

HBV Management Strategies in Pregnancy

- Requiring HBV treatment and considering pregnancy
  - Timing of IFN Rx (if tolerable clinical profile) before pregnancy
  - If clinically stable, can defer treatment until after pregnancy
  - Consider antiviral treatment in 3rd trimester to prevent MTCT
- Pregnant whilst on HBV treatment
  - Consider need for treatment and risk of MTCT
  - Рерс and type of treatment
  - Stop IFN and switch to antivirals
- Pregnant and treatment not clinically indicated for HBV infection
  - Delays treatment until after pregnancy and then resumes need
  - Consider antiviral treatment in 3rd trimester to prevent MTCT
**HBV Treatment in Pregnant Women**

- Indications for Rx in HBV-infected pregnant mother same as usual indications:
  - Active viremia (high HBV DNA levels)
  - Necro-inflammation (raised ALT or other histology)
  - Cirrhosis
- Drug of choice is tenofovir
- Similar rate of birth defects to general population
- Interferon is contraindicated
- Risk of HBV flare - close monitoring required
- Mother is untreated
- If antiviral stopped during pregnancy or soon after delivery

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**HBV Mother-to-Child Transmission**

- Over 60 million new HBV infections per annum
- The majority of infections are acquired in the perinatal/neonatal period or in early childhood
- Perinatal infections are the reservoir of infections in high endemic areas e.g. China, South-East Asia
- Horizontal transmission in early childhood from infected family members (6 months to 5yrs) accounts for most infections in sub-Saharan Africa

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**Perinatal HBV Transmission**

- Perinatal infection occurs:
  - In utero (uncommon)
  - During delivery
  - After birth
  - Breastfeeding (controversial)
Risk Factors for Perinatal HBV Transmission

- HBsAg positive mother
  - >50% risk of infecting child with no treatment
- High maternal HBV DNA (>7.3 log_{10} IU/mL)
- Maternal acute HBV in 2nd or 3rd trimester or within 2 months of delivery
- Risk reduced to <10% with active-passive immunization

Age at HBV Acquisition and Chronicity

Chronicity of HBV determined by age of acquisition of infection

- 90% after neonatal infection (HBsAg positive mothers)
- 20-40% with childhood infection (<5 years of age)
- <5% when acquired in adulthood

Prevention of neonatal & early childhood infection crucial

- Prevents chronicity and subsequent complications of chronic liver disease and HCC

Age at HBV Acquisition and Chronicity (continued)

Figure 3.1: Outcome of hepatitis B infection by age at infection

2019 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection
Prevention of Mother-to-Child Transmission of HBV

- Significant relationship between maternal HBV DNA level and rate of perinatal infection: in infants > 8 log_10 copies/mL or ~ 7.3 log_10 IU/mL.
  - HBeAg positive and positive mothers.
  - Treatment with lamivudine or tenofovir should be considered in 2nd trimester in mothers with high viraemia to prevent MTCT: tenofovir preferred antiviral.
  - If therapy is administered only for prevention of MTCT, may be discontinued within the first 3 months after delivery.
  - Role of elective Caesarean section in preventing HBV MTCT conflicting: not currently recommended.
  - Antiviral therapy for MTCT prevention must be combined with neonatal HBV vaccination.

Prevention of HBV with Vaccination

- Current WHO guidelines recommend universal HBV vaccination.
- WHO recommends birth dose of HBV vaccination in all endemic countries.
- HBV vaccination a HBIG prevents transmission in 80-95% cases.
  - Immediate HBV vaccine given within 24 hours, ideally within 12 hours.
  - Followed by two or three doses to complete the primary series.
  - Subsequent vaccines can be monovalent or combination.
  - Doses 2 and 3 can be given at the same time as DTP.
- Most sub-Saharan African countries administer HBV vaccine at 6, 10, and 14 weeks.

Passive Immunity with HBIG

- HBIG provides temporary immunity: 3-6 months.
- HBIG prophylaxisplus HBV vaccination may be of additional benefit for the following newborns:
  - Mothers HBeAg positive, HBeAg positive.
  - Mothers HBeAg positive, HBeAg negative, high HBV DNA levels.
  - Full-term neonates born to mothers HBeAg positive, HBeAg negative and low HBV DNA levels.
  - Protection against perinatally acquired infection achieved by immediate vaccination against HBV (within 24 hours) may not be significantly improved by the addition of HBIG.
Risk of HBV Transmission from Breastfeeding

- HBsAg detected in breast milk
- HBV vaccination plus HBIG gives protection
- No difference in rates of HBV infection in breastfed versus bottle-fed babies
- Breast feeding not contraindicated
  - stop if cracked or bleeding nipples
  - concern if high maternal HBV DNA
- No data on effects on the infant of exposure to HAs during breastfeeding.

Post-Partum HBV Follow-up

Risk of flares post-partum

- High HBV DNA levels (>4 log10 IU/ml) and interferon-gamma inducible protein-10 levels (>10-200 pg/ml) during the second trimester
- High pretreatment ALT or those treated <1 year before pregnancy have high risk of severe hepatitis flares after cessation of antiviral agents

Important to monitor post delivery for flares

- Mothers not on treatment
- Treatment stopped during pregnancy
- Treatment stopped after delivery

Conclusions: HBV and Pregnancy

- All pregnant women must be tested for HBsAg
- All neonates born to HBsAg positive mothers must receive birth dose of HBV vaccine and complete vaccine series
- High HBV DNA levels, typically observed in HBsAg positive women
  - ≤15% risk of transmission despite HBIG and vaccine prophylaxis
- Consider tenofovir therapy in 2nd trimester to prevent MTCT of HBV
- Indications for HBV therapy in pregnancy are same as for non-pregnant women
- Close follow-up for 6 months post-partum; risk of flares if not on therapy or therapy stopped during pregnancy
_MODULE 6_  
**MANAGEMENT CONSIDERATIONS FOR HIV/HBV COINFECTION**

**TRAINER GUIDE**

**Time Required:**  
Approximately 30 minutes

**Learning Objectives:**  
1. Understand the epidemiology of HIV and HBV  
2. Discuss the impact of HIV/HBV coinfection  
3. Explain the management of HIV/HBV coinfection  
4. Describe guidelines for initiating HIV ART in HIV/HBV coinfection  
5. Describe HBV treatment options in HIV/HBV coinfection

**Supporting Materials:**  
PowerPoint Slides  
Case Study (refer to Learning Activities section)

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**Learning Objectives**

- Understand the epidemiology of HIV and HBV  
- Discuss the impact of HIV/HBV coinfection  
- Explain the management of HIV/HBV coinfection  
- Describe guidelines for initiating HIV ART in HIV/HBV coinfection  
- Describe HBV treatment options in HIV/HBV coinfection
Epidemiology of HIV/HBV in Sub-Saharan Africa

70% of global 34 million PLHIV live in sub-Saharan Africa

- corresponding to regions of high HBV and HIV endemicity

HIV/HBV/Mortality (annual death rate) [www.worldmapper.org] Nov 2012

HIV/HBV vs HIV/HCV Co-infection in Sub-Saharan Africa

- HIV/HBV co-infections tend to outnumber HIV/HCV co-infections
  - chronic HBV co-infection reported in 30% of all HIV positive subjects
  - highest rates in West and Southern African cohorts
  - reflects low prevalence of injection drug use in sub-Saharan Africa
- Liver-related mortality 2x higher in HBV/HIV than HCV/HIV co-infection

HIV/HBV Coinfection in Sub-Saharan Africa

- Independent transmission and acquisition of HBV and HIV
  - HBV generally acquired in childhood under age of 5 years
  - HIV infection occurs later in life, primarily via heterosexual sex
- Series from West, East and South Africa
  - Chronic HBV infection over-represented in HIV patients suggesting shared risk factors or co-transmission events
Epidemiology of HIV/HBV in Sub-Saharan Africa

Shared transmission routes
- HIV and HBV may share transmission routes in infants and children
  - mother-to-child transmission
  - lack of resources for diagnosis & management of blood-borne viruses in pregnancy and per-puerpera period
- Maternal HIV infection increases mother-to-child transmission of HBV (2.5-fold in one West African study) → HIV promoting HBV replication

Impact of HIV/HBV Coinfection

HIV coinfection promotes:
- Increased HBV replication and rates of HBV reactivation
- AFL
- Increased rates of occult HBV
- Chronicity of newly acquired HBV infections
- Progression to fibrosis and cirrhosis
- Hepatocellular carcinoma
- Increased risk of HJV ART hepatotoxicity
- HIV ART-related immune reconstitution hepatitis

Impact of HIV/HBV Coinfection (continued)
- CD4 count <200 cells/mm³ is associated with 16.2-fold increase in risk of liver-related death compared to CD4 count >350 cells/mm³
- Liver disease is leading cause of death in HIV/HBV or HCV coinfection in Western cohorts
- Mortality due to other HIV-related conditions has declined following introduction of HIV ART
- Earlier studies found no consistent evidence for a significant effect of HBV on HIV disease progression
- Recent longitudinal cohort studies → HBV coinfection also leads to increased progression to AIDS-related outcomes and all-cause mortality
Management of HIV/HBV Coinfection

HBV Screening and Vaccination
- All newly diagnosed HIV infected individuals screened for HBV
  - HBSAg and anti-HBs
- Non-immune (HBSAg and anti-HBs negative) - vaccinate
- Lower response to vaccination especially with low CD4 counts
- Meta-analysis - a double dose (40ug) vaccine schedule gives higher protective anti-HBs

Hepatitis A Vaccination
- Should be considered in all HIV-positive patients, especially men who have sex with men
- Screen for Hepatitis C
- Treat HIV/HBV/HDV - Treat the dominant virus
Initiation of HIV ART in HBV Coinfection

2013 WHO ART guidelines recommend initiation of HIV ART in

- All HIV-infected adults with a CD4 count <500 cells/mm³
- Regardless of stage of liver disease
- Individuals with severe chronic liver disease regardless of CD4 count
- At greatest risk of progression and mortality from liver disease
- HIV ART initiation may improve overall survival in cirrhosis
- All pregnant or breastfeeding women regardless of CD4 count
- All children less than 5 years of age regardless of CD4 count

Initiation of HIV ART in HBV Coinfection (continued)

Goal of therapy

- Virological suppression of both HIV and HBV replication
- Amelioration of transaminitis and histological injury and prevention of liver-related complications

Choice of ART regimen in HIV/HBV co-infected patients

- HIV ART regimen containing 2 agents that are also active against HBV
  - reduces the risk of resistance
  - tenofovir + lamivudine/nevirapine + efavirenz as FDC
  - first-line therapy for adults, adolescents and children >5 yrs

Treatment of HIV/HBV Coinfection

Fixed-dose combination (tenofovir, lamivudine/nevirapine and efavirenz)

- HBsAg-positive patients after 5 years of treatment: high rates of
  - HBV DNA suppression (90%)
  - HBsAg loss (46%)
  - HBsAg loss (12%)
  - No evidence of resistance
  - Reduced progression to cirrhosis
  - Risk of HCC remains, but is low
  - No significant difference in response rates compared with HBV monoinfection
HIV/HBV Coinfection Treatment Options

- Monitoring on FDC
  - Tenofovir contraindicated (HIV nephropathy)
  - Little data on the best alternative treatment
  - Consider entecavir as part of HIV ART regimen
    - NRTI: has weak HIV antiretrovirals activity
    - No previous exposure to lamivudine
    - Previous lamivudine, but no evidence of lamivudine-associated HBV polymerase resistance
  - Consider annual assessment of bone function
  - Adjust tenofovir dose according to GFR

HIV/HBV Coinfection Treatment Options (continued)

- Treatment of HIV without the use of tenofovir in the regimen
  - May lead to flares of hepatitis B due to ART-associated RIS
  - Treatment discontinuation, especially lamivudine, associated with
    - HBV reactivation, ALT flares, and hepatic decompensation
  - IFARs need to be changed because of HIV drug resistance/toxicity
    - Tenofovir and lamivudine or tenofovir/telbivudine/tenofovir should be continued together with the new ART drugs

Considerations for HIV/HBV Coinfection Treatment in Children

- Additional management challenges:
  - Choice of HIV ART regimen in children not requiring Rx for HBV
  - Tenofovir cannot be used in children aged <12 years
  - Logistically challenging to use a lamivudine-free regimen
  - Use a standard HIV ART regimen (that may include the use of lamivudine)
    - with subsequent modification to tenofovir-based regimen at age of 12 years
Conclusions: HIV/HBV Coinfection

- Sub-Saharan Africa is the epicenter of HIV and HBV is endemic
  - Increased risk of HIV/HBV coinfection
- HIV promotes chronicity of HBV infection, liver fibrosis, and increases the risk of hepatocellular carcinoma
- Fixed-dose combination of tenofovir + lamivudine/entecavir/tenofovir + etravirine simplifies management of HIV/HBV coinfection regardless of immunologic, virologic, or histologic considerations
- Second-line ART for HIV resistance – important to continue tenofovir, lamivudine/entecavir/tenofovir to prevent HBV reactivation, ALT fibres and potential hepatic decompensation
- HIV ART improves overall survival even in cirrhotics
LEARNING ACTIVITIES

LEARNING ACTIVITY MODULES 1–3

Case Study Application. Teams of two to four trainees are given a patient case study and asked to apply the information learned from Modules 1-3. This team activity is followed by a whole class discussion of each team’s conclusions and responses to the case study questions. This exercise requires approximately one hour to complete.

A 24-year-old student, was referred to the clinic for management of chronic HBV infection. His 32-year-old brother had recently been diagnosed with multifocal hepatocellular carcinoma and was found to be HBsAg positive. On screening our patient was found to HBsAg positive, Hepatitis BeAg positive and HBeAb negative. He was completely asymptomatic.

Social history: Our patient and his siblings had been born in a rural area and their family had relocated to the city when they were in their late teens. Our patient drank mainly over weekends – approximately 20 units of alcohol.

No history of supplements or recreational drugs.

Family history: On further HBV screening of the family: Mother: HBsAg positive, HBeAg negative
Sister: HBsAg negative, HBsAb negative and HB total core Ab positive

Clinically on examination he was not jaundiced, had no peripheral stigmata of chronic liver disease. His liver span was 12 cm and there were no clinical signs of portal hypertension.

FURTHER INVESTIGATIONS

FBC: Hb 14.5 g/dl, WCC 5.2 and platelets 201 x109
Creatinine: 72 umol/l (49-90),
Liver profile: Total Bilirubin 18 umol/l (0-21), Conjugated Bilirubin 9 umol/l (0-6), ALT 72 units/l (5-40), AST 53 units/l (5-40), ALP 118 units/l (40-120), GGT 34 units/l (0-35), Albumin 38 g/l (35-52)
HBV DNA: 3 524 786 IU/ml

QUESTIONS

1. What is the most likely mode of HBV acquisition in our patient?
2. Explain the sister’s serology and in which clinical situation would you want to know whether she had occult hepatitis B?
3. What test would you perform to exclude occult hepatitis B in the sister?
4. What phase of chronic HBV infection does our patient presenting with?
5. What non-invasive tests would you perform to assess the stage of our patient’s liver disease?

6. Is there a role for a liver biopsy?
7. Does our patient require treatment for his hepatitis B – explain your reasons.
8. What HBV treatment option would you consider – explain the reasons for your choice.
9. How would you counsel this patient about his HBV infection?
10. How would you monitor this patient?
11. Is a cure possible in hepatitis B?
12. Explain how chronic infection occurs?
Case Study Application. Teams of two to four trainees are given three patient case studies and asked to apply the information learned from Modules 4-6. This team activity is followed by a whole class discussion of each team’s conclusions and responses to the case study questions. This activity requires approximately one and a half hours to complete.

MODULE 4 - IDENTIFICATION AND MANAGEMENT OF HBV TREATMENT FAILURE

A 45-year-old laborer is known to your clinic with chronic HBV on treatment with lamivudine 150mg daily. He is noted at a routine 6 monthly follow up to have a HBV DNA level of 9 678 IU/ml.

He had first presented 2 years previously with decompenesed liver disease and renal impairment. Clinically he was jaundiced, had a mild flap, small liver (span 9cm) and moderate ascites.

INVESTIGATIONS AT THE STAGE OF INITIAL PRESENTATION

FBC: Hb 11.5 g/dl, WCC 3.2 and platelets 99 x109/l

INR: 1.8

Creatinine: 196 umol/l (49-90)  eGFR 40 ml/min/1.73m2

Liver profile: Total bilirubin 124 umol/l (0-21), conjugated bilirubin 86 umol/l (0-6), ALT 132 units/l (5-40), AST 145 units/l (5-40), ALP 118 units/l (40-120), GGT 46units/l (0-35), albumin 31 g/l (35-52)

HBsAg positive, HBeAg negative, HBeAb positive

HBV DNA: 34 723 IU/ml

Alpha-fetoprotein: 6.7 ug/l (0-7)

Ultrasound liver revealed a small liver (9 cm) with an irregular contour and moderate ascites

In view of his renal impairment, he was started on lamivudine 150mg daily as entecavir was not available. He responded well to treatment, HBV DNA was undetectable at 6 months post initiation of lamivudine. His jaundice had resolved, transaminases and INR had normalized.

Over the next 2 years, he remained well with compensated liver disease and undetectable HBV DNA levels. On further questioning at this clinic visit, the patient admitted that he had recently returned to his home town for 3 months and had run short of lamivudine for 1 month.

Clinically he was well, was not jaundiced, and had no evidence of clinical decompensation. Liver span was 10 cm. No ascites.

Questions:

1. Is this primary or secondary treatment failure and give your reasons?
2. What are the risk factors for treatment failure and drug resistance?
3. Is a rising ALT a good marker for drug resistance?
4. What is the usual progression of events (clinical, biochemical, and virological) in the emergence of drug resistance?
5. In the absence of HBV DNA testing, how would you suspect treatment failure and drug resistance?
6. What is the risk of resistance with lamivudine?
7. How would you confirm that this patient had lamivudine resistance?
8. Is it necessary to confirm resistance or could you just change to an antiviral with a high genetic barrier to resistance? Give your reasons.
9. In this patient, which antiviral would you choose and would you add on to his lamivudine or would you just switch antivirals?
10. How do you counsel a patient pre-initiation of antivirals and how do you monitor adherence?
11. With clinical deterioration and rising HBV DNA levels in the setting of tenofovir use, is this likely to be due to tenofovir resistance and/or what other causes should be considered?
MODULE 5: PREGNANCY AND HEPATITIS B

A 24-year-old woman who is known to your clinic with chronic HBV (immune tolerant) presents 3 months pregnant at a routine follow-up visit. She is asymptomatic, but is concerned about HBV transmission to the baby.

Clinically, she is not jaundiced, has mild palmar erythema, but no other stigmata of chronic liver disease. Liver span is 11 cm and there are no signs of portal hypertension. BP 110/70. Urine dipstix normal.

FURTHER INVESTIGATIONS

FBC: Hb 11.5 g/dl, WCC 6.2 and platelets 258 x10^9/l

INR: 0.8

Creatinine: 55 umol/l (49-90)

Liver profile: Total bilirubin 11 umol/l (0-21), conjugated bilirubin 5 umol/l (0-6), ALT 14 units/l (5-40), AST 13 units/l (5-40), ALP 128 units/l (40-120), GGT 24 units/l (0-35), albumin 35 g/l (35-52)

HBsAg positive, HBeAg positive, HBeAb positive

HBV DNA: 15 347 486 IU/ml

HIV: Negative

Alpha-fetoprotein: 457 ug/l (0-7)


QUESTIONS

1. What is the natural history of hepatitis B in pregnancy and do you need to follow up the mother more frequently?
2. Are there any potential adverse pregnancy outcomes?
3. What are the risks of perinatal HBV transmission in this patient?
4. Does this mother need to be started on treatment for her hepatitis B and are the indications for HBV treatment different in pregnancy?
5. Are you concerned about the elevated Alpha-fetoprotein and the albumin level at the lower limit of normal?
6. If she does not require treatment for her hepatitis B, would you consider mother-to-child prophylaxis (MTCP) and when would you start this?
7. What treatment would you give for MTCP and do you need to continue this treatment after delivery? If treatment not needed post-delivery when would you stop treatment?
8. Is MTCP sufficient to prevent HBV perinatal transmission?
9. What prophylactic immunization regimen is recommended to prevent perinatal HBV transmission? Explain the timing of prophylactic immunization and the mode of administration including the potential role of HBIG.
10. Is elective Cesarean section recommended to reduce the risk of perinatal transmission?
11. If perinatal HBV transmission occurs, what is the risk of neonatal chronic HBV infection?
12. Is breastfeeding contraindicated?
13. How would you follow up this mother post-delivery?
Ms. SD, a 25-year-old machinist, presents to her local healthcare facility complaining of weight loss and night sweats. She is found to be gene expert positive for mycobacterium tuberculosis and on further screening she is HIV positive with a CD4 count of 95 cells/mm³.

FURTHER INVESTIGATIONS PRIOR TO INITIATION OF TB TREATMENT

Liver profile: Total bilirubin 22 umol/l (0-21), conjugated bilirubin 15 umol/l (0-6), ALT 62 units/l (5-40), AST 55 units/l (5-40), ALP 143 units/l (40-120), GGT 66 units/l (0-35), albumin 32 g/l (35-52)
Creatinine: 74 umol/l (49-90)
HBsAg positive, HBeAg positive, HBeAb negative
HBV DNA: 207 643 IU/ml

TB treatment was initiated with rifafour and 2 weeks later, ART as a fixed-dose combination of tenofovir/emtricitabine and efavirenz was started. There had been no liver enzyme deterioration on TB treatment.

One month after initiation of ART, she presented complaining of jaundice and fever. Of note at the local HIV clinic, she had also been started on cotrimoxazole for pneumocystis prophylaxis. Clinically she was jaundiced, not encephalopathic and liver was palpable 3 cm below the costal margin (span 16 cm).

INVESTIGATIONS

FBC: Hb 11.6 g/dl, WCC 3.4 and platelets 168 x10^9 /l
INR: 1.3
Liver profile: Total bilirubin 89 umol/l (0-21), conjugated bilirubin 73 umol/l (0-6), ALT 162 units/l (5-40), AST 145 units/l (5-40), ALP 343 units/l (40-120), GGT 186 units/l (0-35), albumin 32 g/l (35-52)
Creatinine: 118 umol/l (49-90)

Ultrasound liver revealed an enlarged, echogenic liver with no focal lesions. There were splenic micro-abscesses, but no significant lymphadenopathy.

Liver biopsy confirmed features compatible with a TB IRIS.

TB treatment and the FDC were continued and over the next month, her liver profile normalized.

Three years later, she was referred back with HBV and HIV virological failure (as a result of non-adherence) for assessment for an appropriate new HIV ARV regimen.

QUESTIONS

1. What are the potential modes of acquisition of HBV/HIV coinfection in this patient?
2. What is more common in sub-Saharan Africa – HBV/HIV or HCV/HIV coinfection? Explain potential reasons. Which has a higher liver related mortality?
3. How does HIV impact on the natural history of hepatitis B?
4. Does hepatitis B impact on HIV disease progression?
5. What are the WHO guidelines for the initiation of HIV ARV treatment in HIV/HBV coinfection?
6. Are women who are HIV/HBV-coinfected at greater risk of mother to child transmission of hepatitis B than mothers who are HBV monoinfected?

7. Why was the liver biopsy useful in establishing the cause of the deterioration of liver enzymes in this patient? What other etiologies for the deterioration of liver enzymes should you consider?
8. Has the use of an FDC been shown to have any long-term beneficial effects on the natural history of hepatitis B?
9. Why should tenofovir and lamivudine be continued as part of the new HIV ARV regimen?
10. How do you monitor patients on a FDC?
PATIENT EDUCATION

What is hepatitis B?

- Hepatitis B is a liver disease caused by the hepatitis B virus (HBV) and can be both an acute and chronic disease.
- In 90% of adults, HBV can be cleared on its own. But, if contracted early in childhood, it becomes chronic in 90% of cases and treatment is necessary.
- Two billion people worldwide (or 28% of the population) have been infected with HBV and about 600,000 people die every year due to the consequences of hepatitis B.

How is hepatitis B virus spread?

HBV is spread through contact with the blood, semen, or vaginal fluid of an infected person.

Who is at risk of getting hepatitis B?

Those at risk of contracting hepatitis B include people who:

- have multiple sexual partners;
- were born to mothers who have hepatitis B;
- have family members with hepatitis B;
- use injection drugs;
- have an occupation involving increased exposure to blood and body fluids; and
- live in or travel to countries that have a high prevalence of hepatitis B (Asia, sub-Saharan Africa, Southern and Eastern Europe, and the Pacific Islands).

What are the symptoms of hepatitis B?

- Many people who have hepatitis B do not experience any symptoms.
- The symptoms can include jaundice (skin and eyes turn yellow), fatigue, loss of appetite, fever, rash, and acute arthritis.
- Chronic hepatitis B can lead to cirrhosis (scarring of the liver) and liver cancer.

Is hepatitis B a preventable disease?

To prevent getting hepatitis B, it is important to get vaccinated. Two to three injections of the vaccine within a six-month period provide long-lasting protection against the virus. The vaccine can be accessed free of charge with the help of a healthcare provider.

Hepatitis B can also be prevented by:

- Consistent condom use;
- Screening all pregnant women and, if the mother is infected, administering both the first dose of the vaccine and HBlg (protective antibody called immunoglobulin) at birth to the baby; and
- Administering HBlg to any person who has had recent exposure (seven to 14 days) with infected blood or body fluids.

To prevent the spread of the virus to others, people with HBV should:

- Use condoms consistently;
- Never share toothbrushes, razors, nail files, or other items that may contain traces of blood;
- Never donate blood or semen;
- Get rid of articles contaminated with blood by placing them in a protective container;
- Cover all cuts and sores with band-aids; and
- Clean up spills of their blood with a bleach solution.

If a woman is pregnant or planning to have children, she should know that there is a high risk of passing the virus on to the baby around the time of birth. The baby can be protected through immunization, so he or she should receive the vaccine against HBV right at birth.

Medication also helps reduce the risk of passing the virus on to others so it is important for people to take it as prescribed.
How is hepatitis B infection diagnosed?

Hepatitis B infection is diagnosed through blood tests.

Is there a treatment for hepatitis B?

There is no cure for chronic hepatitis B. However, individuals have several treatment options to prevent the development of cirrhosis, liver failure, or liver cancer.

Patients should discuss available HBV treatment options with their physician.

What else can people do to live well with hepatitis B?

- Get vaccinated against hepatitis A (HAV);
- Implement lifestyle changes, such as maintaining a healthy body weight, eating a well-balanced diet, exercising regularly, quitting smoking, and avoiding alcohol and high-risk behaviors;
- Know that no alternative therapies – including herbal remedies, homeopathic medicines, and minerals – have been proven safe and effective for HBV treatment;
- Inform their healthcare provider of any medication taken for other conditions because some medication may affect the outcome of HBV treatment (e.g., some drugs are harmful to the liver).