TRAIN-THE-TRAINER MANUAL

HBV CLINICAL MANAGEMENT

AFRICAN REGIONAL CAPACITY-BUILDING HUB

IAPAC

Supported through a restricted educational grant from Gilead Sciences.

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.

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PREFACE

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).

IAPAC INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE

IASL International Association for the Study of the Liver

WE BUILD FOR THE FUTURE

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SPES BONA

CONTENTS

ACRONYMS

AASLD	American Association for the Study of Liver Disease
ALF	acute liver failure
ALT	alanine aminotransferase
Anti-HBc (HBcAb)	hepatitis B core antibody
Anti-HBe (HBeAb)	hepatitis B e-antibody
Anti-HBs (HBsAb)	hepatitis B surface antibody
APRI	aspartate aminotransferase to platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BMI	body mass index
CAR	Central African Republic
cccDNA	covalently closed circular DNA
CD4	cluster of differentiation 4
CHB	chronic hepatitis B
CrCl	creatinine clearance
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
dsDNA	double-stranded DNA
DTP	diphtheria–tetanus–pertussis
eAg	e-Antigen
EASL	European Association for the Study of the Liver
ER	endoplasmic Reticulum
FDC	fixed-dose combination
GFR	glomerular filtration rate
gGT	Gamma glutamyl transpeptidase
HAV	hepatitis A Virus
HBcAg	hepatitis B core antigen
HBIG	hepatitis B immune globulin
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBx Protein	hepatitis B virus X protein
HCC	heptocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
IAPAC	International Association of Providers of AIDS Care
IFN	interferon
IgG core Ab	immunoglobulin G core antibody
IgM core Ab	immunoglobulin M core antibody
IRIS	immune reconstitution inflammatory syndrome
LMIC	low- and middle-income countries
MTCT	mother-to-child transmission
mRNA	messenger RNA
NAs	nucleos(t)ide analogues
NIT	non-invasive test
NMA	network meta-analysis
pegIFN	peginterferon
PLHIV	people living with HIV
PPV	positive predictive value
RCT	randomized controlled trial
RNA	ribonucleic acid
sSA	sub-Saharan Africa
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal
WHO	World Health Organization

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

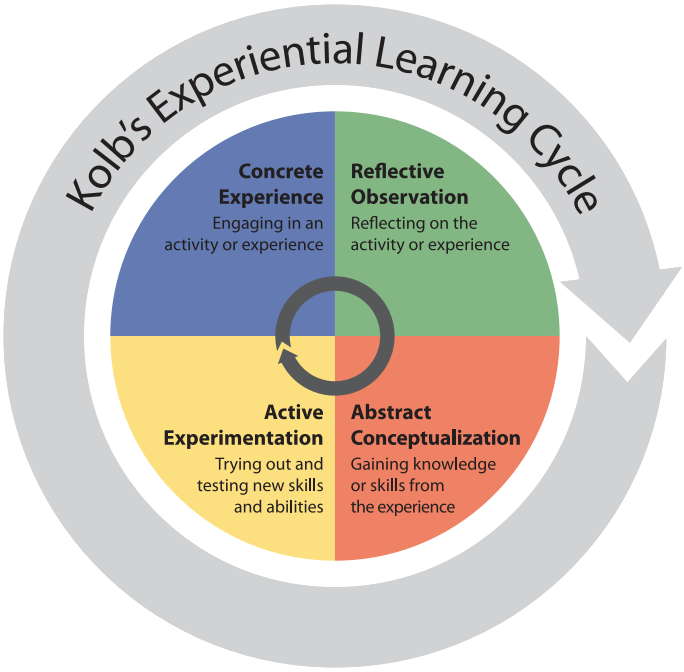
LEARNING CYCLE

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



© 2014 SkillsYouNeed.com Kolb D.A. (1984) "Experiential Learning experience as a source of learning and development," New Jersey: Prentice Hall.

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 to 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:

KNOWLEDGE	COMPREHENSION	APPLICATION
Define	Explain	Apply
List	Express	Employ
Recognize	Describe	Demonstrate
Record	Discuss	Illustrate
Repeat	Identify	Interpret
State	Restate	Perform
	Translate	Practice
		Use

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?

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:

a. aim(s)/goal(s)/purpose
b. specific objectives
c. course content
d. training methods/pedagogy
e. timeframe for the training
f. 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.

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.

DATE:

FACILITY, CITY, COUNTRY:

8:00 AM– 9:00 AM	Registration/Check-In/Breakfast
9:00 AM– 9:15 AM	Welcome, Introductions, and Training Overview
9:15 AM– 9:45 AM	**Module 1: Hepatitis B Virology**
9:45 AM– 10:15 AM	**Module 2: Assessment of Liver Disease Stage**
10:15 AM– 11:00 AM	**Module 3: First-Line Treatment of Chronic HBV**
11:00 AM– 11:30 AM	Break
11:30 AM– 12:30 PM	**Learning Activity: Case Study Application**
12:30 PM– 1:30 PM	Lunch
1:30 PM– 2:15 PM	**Module 4: Identifcation and Management of HBV Treatment Failure**
2:!5 PM– 2:45 PM	**Module 5: HBV and Pregnancy Management Considerations**
2:45 PM– 3:15 PM	**Module 6: Management Considerations for HIV/HBV Coinfection**
3:15 pM– 3:30 PM	Break
3:30 PM– 4:30 PM	**Learning Activity: Case Study Application**
4:30 PM– 5:00 PM	**Summary and Evaluation**
5:00 PM	Adjourn

TRAINER 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':

- **G**ives (what participants can give to the course)
- **G**ains (what they hope to gain from the course)
- **G**hastlies (what they hope does not happen in the course (e.g., too simple, too advanced, not relevant, etc.)
- **G**round 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.

MODULE 1

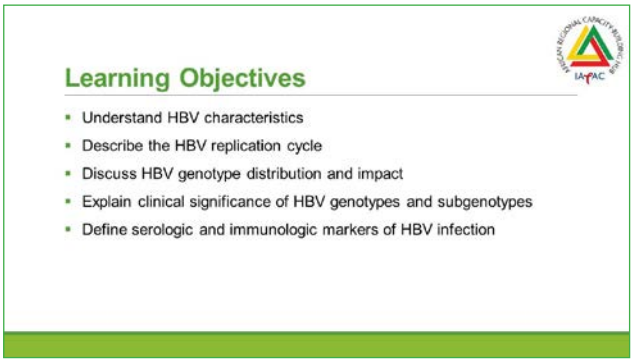
HEPATITIS B VIROLOGY

TRAINER GUIDE

Time Required:
Approximately 30 minutes

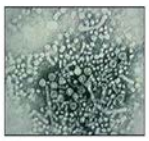
Learning Objectives:
1. Understand HBV characteristics
2. Describe the HBV replication cycle
3. Discuss HBV genotype distribution and impact
4. Explain the clinical significance of HBV genotypes and subgenotypes
5. Define the serologic and immunologic markers of HBV infection

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

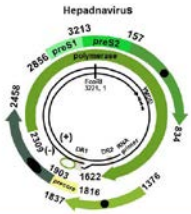


Hepatitis B Virus

- 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



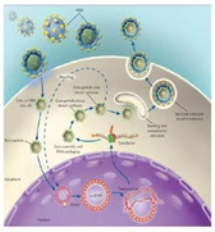
HBV Genome



- Enveloped partially dsDNA virus (42nm)
- Compact genomic structure (± 3.2 kb)
- 4 overlapping open reading frames
- Reverse transcriptase/ DNA polymerase domain overlaps with surface gene
- Encodes 4 sets of viral proteins – HBsAg, HB core Ag, viral polymerase and HBx protein

MMWR 2003;52:1-33. Ott MJ and Ahuda M. J Pediatr Health Care. 1999;13:211-216. Ribeiro RM, et al. Microbes and Infection. 2002;4:829-835

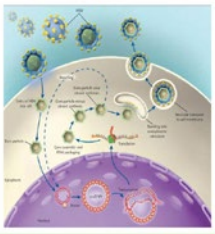
HBV Replication Cycle



1. HBV virions bind to the hepatocyte receptor – *sodium taurocholate co-transporting polypeptide* – and are internalized
2. In nucleus genome repaired to form cccDNA
3. Translation of viral mRNA to proteins in cytoplasm

NEJM March 2004, 350:11

HBV Replication Cycle (continued)



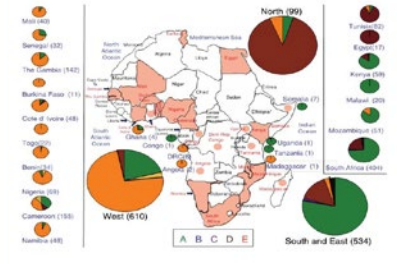
4. Incorporation into ER and reverse transcription of RNA
5. Budding and secretion of of viral cores to ER, and packaging in Golgi apparatus **or**
6. Recycling of genome to nucleus with repletion of intranuclear cccDNA

NEJM March 2004, 350:11

Geographic Distribution: HBV Genotypes

Alexandre Valsamakis Clin. Microbiol. Rev. 2007;20:426-439

HBV Genotypes in Africa



Hepatology Research 2007; 37: 93-103

Impact of HBV Genotype on Disease Progression

Genotype C

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

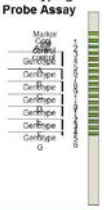
Genotype

- 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

HBV Genotyping Line Probe Assay



Keeffe EB, et al. Clin Gastroenterol Hepatol. 2006;4:936-962.

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 6.5 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

Variable	Genotypes B	Genotypes C
Presence of HBeAg	Low	High
Spontaneous HBeAg seroconversion	Early	Late
Histological activity	Low	High
Rate of progression to cirrhosis	Low	High
Risk of hepatocellular carcinoma	Low (Japan, China) Variable (Taiwan)	High
Response to interferon	High	Low
Response to nucleotide(side) therapy	Similar	Similar

From UpToDate – adapted from Anna SF Lok, MD and Chi Jen Chu, MD

HBV Serologic Markers

HBsAg

- General infection marker
- First serologic marker to appear
- Infection considered chronic if persistent for > 6 months
- Indicative 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 HBeAg negative disease

Anti-HBc total (HBcAb total)

IgG core Ab

- Past exposure to HBV

IgM Core Ab

- Acute infection or reactivation

Immunologic Markers: Chronic HBV Infection

Marker	Immune Tolerant	Chronic HBV Disease		Immune control	Occult HBV
		Immune Clearance HBeAg Positive	Immune Escape HBeAg Negative		
HBsAg	✓	✓	✓	✓	
HBeAg	✓	✓			
Anti-HBe			✓	✓	
Anti-HBc IgG	✓	✓	✓	✓	✓
HBV DNA IU/ml	>200 000	>20 000	> 2 000	< 2 000	< 200
ALT	Normal	↑	↑	Normal	Normal

Keeffe EB, et al. Clin Gastroenterol Hepatol. 2006;4:936-962; Lok AS, et al. Hepatology 2007;45:507

Conclusions: HBV Virology

- HBV is a hepatotrophic, oncogenic virus
- Sodium taurocholate co-transporting polypeptide is the newly identified hepatocyte receptor for HBV
- Replicative life cycle – cccDNA 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

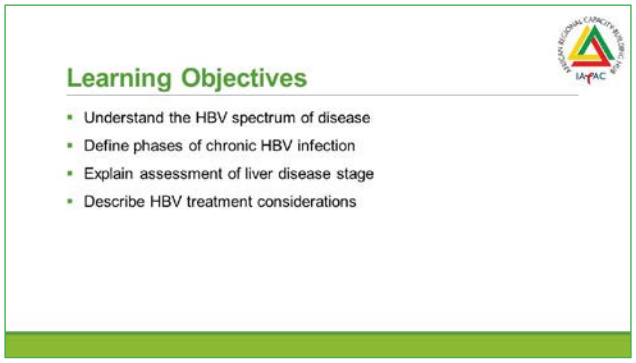
ASSESSMENT OF LIVER DISEASE STAGE & HBV TREATMENT CONSIDERATIONS

TRAINER GUIDE

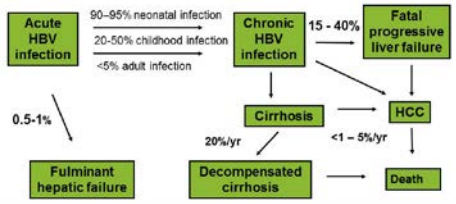
Time Required:
Approximately 20 minutes

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

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

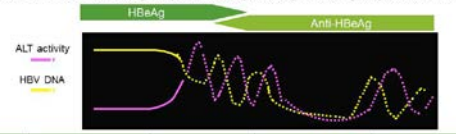


Spectrum of Disease



Phases of Chronic HBV Infection

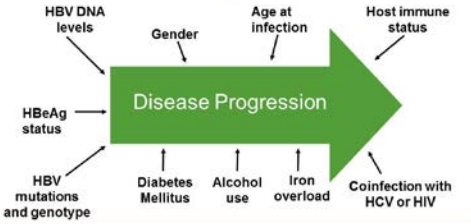
Natural history dynamic and complex. Phases have variable duration and are not necessarily sequential. All phases potentially require treatment.



Phase	Immune Tolerant	Immune Active	Immune Control	Immune Escape
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation and progressive fibrosis

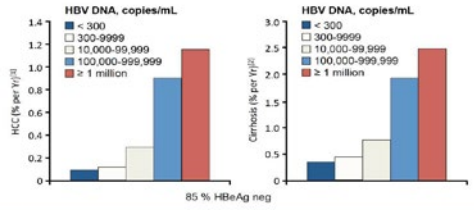
Yim HJ, et al. Hepatology. 2006;43:S173-S181

Factors Influencing Natural History



REVEAL Study

Risk of HCC and Cirrhosis According to Baseline HBV DNA



1. Chen CJ, et al. JAMA. 2006;295:65-73. 2. Iloeje UH, et al. Gastroenterology 2006;130:678-686.

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 co-factors
- Standardised biopsy scoring systems - *METAVIR and Knodell and Ishak scores*

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

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 NITs in resource-limited settings

- Will help with optimal selection of persons with CHB for antiviral Rx
- Few validated studies in sSA

Assessment of Liver Disease Stage (continued)

APRI and Fib-4

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

Fibrotest

- Patented commercial test
- Expensive
- Accredited laboratory

NITs 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 ≥ 2
- 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)

Test	Components	Fibrosis stages assessed	Requirements	Cost
APRI	AST, platelets	≥F2, F4 (cirrhosis)	Basic haematology and clinical chemistry	+
FIB-4	Age, AST, ALT, platelets	≥F3	Basic haematology and clinical chemistry	+
FibroTest	Gamma glutamyl transpeptidase (gGT), haptoglobin, bilirubin, A1 apolipopotein, alpha2-macroglobulin	≥F2, ≥F3, F4 (cirrhosis)	Specialized tests. Requires testing at designated laboratories. Commercial assay	+ +
FibroScan	Transient elastography	≥F2, ≥F3, F4 (cirrhosis)	Dedicated equipment	+ + +

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

Assessment of Liver Disease Stage (continued)

Results of NITs may be impacted by intercurrent diseases that may falsely increase or decrease the scores:

- 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 flares 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

Fibroscan and APRI

- Most useful tests for assessing cirrhosis in LMICs (conditional recommendation)
- PPV for detection of cirrhosis was low for all NITs, 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 not cirrhosis

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

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

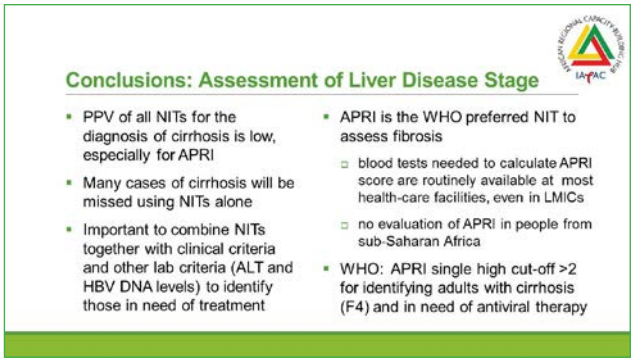
- Interferon (IFN)-based therapy
- Nucleos(t)ide analogue therapy

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 NITs for the diagnosis of cirrhosis is low, especially for APRI
Many cases of cirrhosis will be missed using NITs alone
Important to combine NITs 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 NIT to assess fibrosis
blood tests needed to calculate APRI score are routinely available at most health-care facilities, even in LMICs
no evaluation of APRI in people from sub-Saharan Africa
WHO: APRI single high cut-off >2 for identifying adults with cirrhosis (F4) and in need of antiviral therapy

MODULE 3

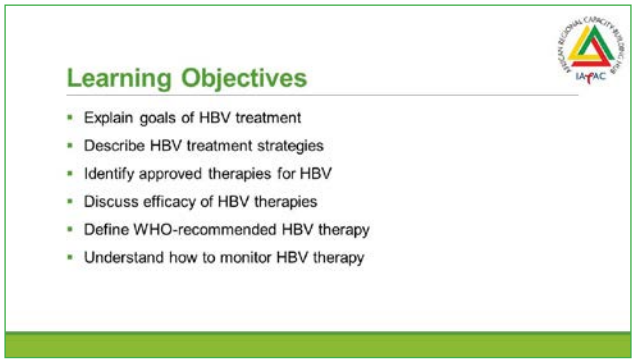
FIRST-LINE TREATMENT OF CHRONIC HBV

TRAINER GUIDE

Time Required:
Approximately 45 minutes

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

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



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: normalisation of serum ALT
- Virological
  - Durable suppression to undetectable HBV DNA
  - Durable HBeAg loss or seroconversion to anti-Hbe
  - Durable HBsAg loss seroconversion to anti-HBs status
- Histological
  - Decrease in necro-inflammatory score
  - Possibly regression of fibrosis on liver biopsy

Goals of HBV Treatment (continued)

HBsAg clearance is the ideal endpoint of therapy

- Aim to reduce number of infected hepatocytes & reduce HBV viral replication level
- ***HBsAg serum levels reflect the transcriptionally active cccDNA***
- ***HBsAg serum levels lowest in immune control phase***
- HBsAg clearance is associated with:
  - reduced incidence of cirrhosis
  - reduced incidence of HCC
  - improved survival

Gut 2002;50(1):100

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** (HBsAg +, HBeAg, and HBV DNA <2,000 IU/ml) through dual mode 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 monoinfection
- Entecavir not widely available, no generics

Clinical efficacy : HBeAg pos	Lamivudine	Adefovir	Telbivudine	Entecavir	Tenofovir	PegIFN
Log_{10} HBV DNA decline at 1yr	5.54	3.5	6.45	6.9	6.4	4.5
HBV DNA undetectable (%) at 1 yr	40-44	13-21	60	67	76	25
ALT normalization (%) at 1yr	60-75	48-54	77	68	68	39
Histologic improvement (%) at 1yr	56-62	53-68	64.7	72	74	38
HBeAg seroconversion (%)						
1 year	18-21.5	12-18	22.5	21	21	27
2 year	27	NA	29.6	31	NA	42
3 year	40	NA	46	NA	26	NA
4 year	47	NA	NA	NA	29	45
5 year	65	48	NA	NA	NA	NA
8 year					31	
HBsAg loss/seroconversion (%)						
1 year	1	0	NA	2	3.2	3-6
2 year	2.8	NA	NA	5.1	NA	NA
3 year	NA	NA	NA	NA	8	11
4 year					10.8	11
8 year					10	

Liver Int 2014;34 (S1):112. Abstract 229. AASLD 2014

HBeAg Negative Chronic HBV

Therapeutic Endpoints	Placebo	Lamivudine	Adefovir	Telbivudine[a]	Entecavir	TDF[b]	Peg-IFN
Undetectable HBV DNA	10 - 20%	60 - 73%	51%	88%	90%	93%	63%
Loss of HBsAg	0 - 1.5%	0%	NR	<1%	<1%	0%	3%[c]
ALT normalisation	0 - 6%	60 - 79%[c]	72%	74%	78%	76%	38%
Histologic improvement	23 - 25%	60 - 66%[c]	64%	67%	70%	72%	59%[c]

All responses at 48 weeks, unless otherwise noted
a. 52 week data
b. Marcellin P, et al. N Engl J Med. 2008; 359: 2442 – 59
c. At 48 weeks at end of therapy and 72 weeks (24 weeks after end of therapy)
d. At 48 weeks and 52 weeks into therapy

Adapted from: Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009; 50: 661 – 2; Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, Tobias H. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update.

Factors Favoring IFN as Initial Therapy

- Favorable predictors of response
  - Genotype A or B > C or D
  - Low HBV DNA
    - ~ baseline <$2x10^5$ - $2x10^8$ IU/mL
    - ~ 12 weeks <20 000 IU/mL
  - High ALT (baseline) >2-5x ULN
  - High activity scores on biopsy (≥A2)
- Specific patient demographics
  - Younger individuals
  - Young woman wanting future pregnancy
- Patient preference
- No coinfection with HIV
- Concomitant HCV or HDV infection

J Hepatol 2012; 57(1):167-85

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 finite 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 HBV Rx candidates in sub-Saharan Africa not suitable for IFN-based Rx

2015 WHO HBV Guidelines recommend entecavir and tenofovi) as first-line Rx

Efficacy: Tenofovir and Entecavir

Network meta-analysis

- 21 pair-wise comparison RCTs comprising 5073 HBeAg positive nucleoside-naïve persons
- 16 trials comprising 2604 HBeAgnegative nucleoside-naïve persons

Tenofovir monotherapy had highest probability of achieving undetectable HBV DNA at end of 1 year of Rx

- HBeAg-positive 94.1% (95% CI: 74.7–98.9%)
- HBeAg-negative 97.6% (95% CI: 56.7–99.9%)

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

Efficacy: Tenofovir and Entecavir (continued)

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

- HBeAg-positive 64.5% (95% CI: 49.1–80.5%)
- HBeAg-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 3.8%
  - Tenofovir : 0.7% and 1.4%
- HCC
  - Entecavir: 3.9% and 6.6%
  - Tenofovir: 1.4% and 2.4%
- Genotypic resistance
  - Entecavir at 5 years of Rx (0.8-1.2%)
  - Tenofovir: no resistance at 8 years

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

Recommended NAs and Dosages for Adults

Drug	Dose
Tenofovir	300 mg[a] once daily
Tenofovir plus emtricitabine	Tenofovir 245 mg, emtricitabine 200 mg
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease)	1 mg once daily

[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir with reduced renal and bone toxicities compared to tenofovir.

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

Recommended NAs and Dosages for Children

Drug	Dose	
Tenofovir (in children 12 years of age and older, and weighing at least 35 kg)	300 mg once daily	
Entecavir (in children 2 years of age or older and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg)	Recommended once-daily dose of oral solution (mL)	
	Body weight (kg)	Treatment-naive persons[1]
	10 to 11	3
	>11 to 14	4
	>14 to 17	5
	>17 to 20	6
	>20 to 23	7
	>23 to 26	8
	>26 to 30	9
	>30	10

[1] Children with body weight more than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

2015 WHO Guidelines for the Prevention, Care and Treatment of Persons with Hepatitis B Virus Infection

Assessment Prior to Treatment Initiation

- Assess severity of chronic liver disease
- Assessment of the level of viral replication
  - HBV DNA, HBeAg and HBeAb 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

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
  - CrCl <50 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
  - concomitant 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
- concomitant nephrotoxic drugs

Monitoring should be more frequent in those at higher risk of renal dysfunction

Monitoring Long-Term NA Therapy

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:

- HBeAg 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 (20% 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
  - 3rd 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

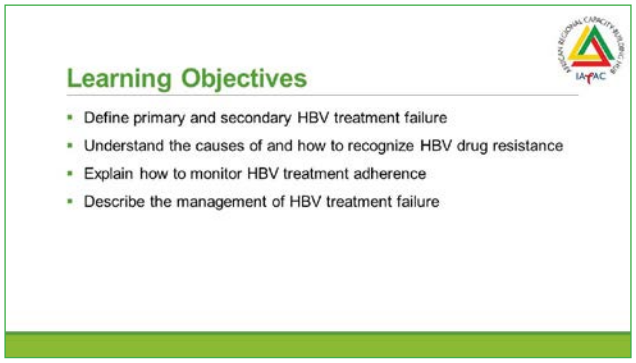
IDENTIFICATION AND MANAGEMENT OF HBV TREATMENT FAILURE

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)



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 adherent to entecavir or tenofovir Rx
- Can occur in persons treated with lamivudine, adefovir or telbivudine

Identifying HBV Treatment Failure (continued)

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)

Identifying HBV Treatment Failure (continued)

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

World J Gastroenterol 2010; 16(37): 4691

Identifying HBV Treatment Failure (continued)

Confirmation of antiviral drug failure

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

World J Gastroenterol 2010;16937):4691

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^{10-12} 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

Hepatology 2007; 46(1):254; Hepatol Int 2008;2:147

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 telbivudine) 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

Virol J 2011;8(1):75; Pharmazie 2012;67(11):883; N Engl J Med 2008;359(23):2442; World J Gastroenterol 2013;19(39):6660; J Clin Pharmacol 2014;54(2):199

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

Gastroenterol 2003;125(6):1714

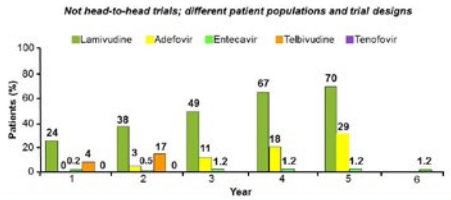
Approved NAs: HBV Treatment

- **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 monoinfection
- 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

J Virus Erad, 2015;1:103

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



EASL clinical practice guidelines. J Hepatol. 2009;50:227-242. Tenney DJ, et al. EASL; 2009; Copenhagen, Denmark. Abstract 20.

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

Counseling

- 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 refills 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 : HBeAg positive patients

- Seven RCTs of pair-wise comparisons based on 919 lamivudine-resistant persons were included for outcome of undetectable HBV DNA (<300 copies/mL or 60 IU/mL)
- Six studies (771 persons) for the outcome of HBeAg seroconversion

Treatments evaluated in HBeAg positive pts

- Switch to an NA with a high barrier to resistance
- Continuation with or add-on therapy

Included the following agents:

- Tenofovir, entecavir, adefovir, lamivudine
- Telbivudine and emtricitabine (in combination with tenofovir)

Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults [CG165]. London: National Institute for Health and Care Excellence; 2013.

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 (66.2% and 33.8%, respectively)
- HBeAg seroconversion (39.8% and 31.2%, respectively) at the end of 1 year of treatment among all the evaluated treatments

After 1 year of tenofovir treatment:

- 89% (95% CI: 51.8–98.2%) of lamivudine-resistant patients would be expected to achieve undetectable HBV DNA
- 17.6% (95% CI: 1.4–74.9%) HBeAg seroconversion
- No NMA was conducted for lamivudine-resistant HBeAg-negative persons

Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults [CG165]. London: National Institute for Health and Care Excellence; 2013.

Management of Lamivudine Resistance

2015 WHO Guidelines recommend switch to tenofovir monotherapy (HBeAg+/- patients)

- Highest probability at 1 year of achieving low/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
  - avoids selection of further compensatory mutations and development of drug resistance, with reservoirs of resistant HBV mutants

AIDS 2002;16(1):131

Management of Lamivudine Resistance (continued)

- *Lamivudine resistance (L180M + M204V/I) 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

AIDS 2002;16(1):131

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 tenofovir

Exclude other causes of clinical deterioration

- DILI
- Other viral infections
- Development of HCC

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

Management of Resistance

Tenofovir monotherapy

- Highest probability at 1yr of achieving low or 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 shares no cross-resistance avoids selection of further compensatory mutations and development of drug resistance, with reservoirs of resistant HBV mutants
- Simplifies clinical management and drug procurement in persons who have developed resistance to lamivudine, adefovir, telbivudine or entecavir

MODULE 5

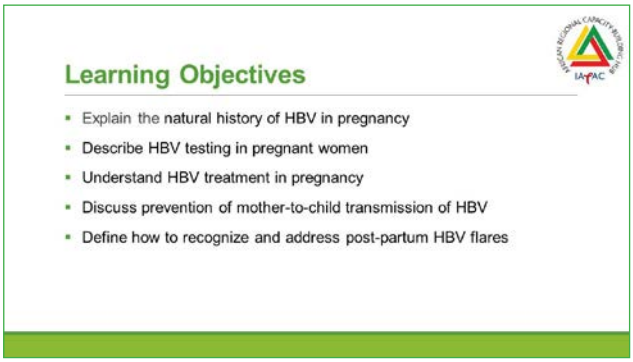
HBV AND PREGNANCY MANAGEMENT CONSIDERATIONS

TRAINER GUIDE

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
- Case reports suggest HBV reactivation, hepatic exacerbations and fulminant liver failure may occur

Adverse pregnancy outcomes – some reports of higher rates of:

- Preterm births
- Gestational diabetes
- Antepartum hemorrhage

HBsAg positive mothers need close follow up during pregnancy

Semin Liver Dis. 2007 Aug;27 Suppl 1:18; World J Gastroenterol. 2004 Aug 1;10(15):2305; Lancet. 1991 Feb 9;337(8737):364; J Hepatol. 2005 Nov;43(5):7717; J Hepatol. 2007 Jul;47(1):46

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

Hepatology 2009 50(3):661; J Hepatol 2012;57(1):167

HBV Management Strategies in Pregnancy

Requiring HBV treatment and considering pregnancy

- Finite course IFN Rx (if favorable 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
- Review type of treatment
- Stop IFN and switch to antivirals

Pregnant and treatment not clinically indicated for HBV infection

- Defer treatment until after pregnancy and then reassess need
- Consider antiviral treatment in 3rd trimester to prevent MTCT

Clin Infect Dis. 2008;46(3):367; Hepatology 2009 50(3):661; J Hepatol 2012;57(1):167

HBV Treatment in Pregnant Women

- Indications for Rx in HBV-infected pregnant mother same as usual indications:
  - active viraemia (high HBV DNA levels)
  - necro-inflammation (raised ALT or on 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 antivirals stopped during pregnancy or soon after delivery

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization 2013; Hepatology 2009;50(3):661; J Hepatol 2012;57(1):167

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

Perinatal HBV Transmission

Perinatal infection occurs:

- In utero (uncommon)
- During delivery
- After birth
- Breastfeeding (controversial)

J Med Virol 2002;67(1):20

Risk Factors for Perinatal HBV Transmission

- HBeAg positive mother
  - >90% 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

J Viral Hepat 2009;16(2):94; J Viral Hepat 2003;10(4):294

Age at HBV Acquisition and Chronicity

Chronicity of HBV determined by age of acquisition of infection

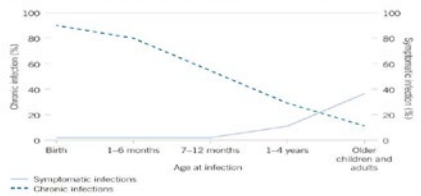
- 90% after neonatal infection (HBeAg positive mothers)
- 20-60% with childhood infection (<5 years of age)
- <5% when acquired in adulthood

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



2015 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 persistent infection in infant (> 8 $\log_{10}$ copies/mL or ~ 7.3 $\log_{10}$ IU/mL)

- HBeAg negative and positive mothers
- Treatment with lamivudine or tenofovir should be considered in 3rd 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 Cesarean section in preventing HBV MTCT conflicting; not currently recommended
- **Antiviral therapy for MTCT prevention must be combined with neonatal HBV vaccination**

Clin Gastroenterol Hepatol 2013; 11(10):1349; BMC Pregnancy Childbirth. 2013 May 24;13:119;J Hepatol 2012;57(1):167; J Hepatol 2012;57(1):167; J Viral Hepat. 2003;10(4):294

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 ± HBIG prevents transmission in 80-95% cases
  - monovalent 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 three can be given at the same time as DTP
- Most sub-Saharan African countries administer HBV vaccine at 6, 10, and 14 weeks

2015 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection; WHO Wkly Epidemiol Rec 2009;84(40):405; Vaccine 2013; 31(Supplement 2): B61

Passive Immunity with HBIG

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

2015 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection

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 NAs during breastfeeding

Obstet Gynecol 2002;99(6):1049; Clin Pharmacokinet 1999;36(1):41; Obstet Gynecol. 2001;98(5 Pt 2):909; MMWR Recomm Rep. 2006 Dec 23;54(RR-16):1-31.

Post-Partum HBV Follow-up

Risk of flares post-partum

- High HBV DNA levels (>4 $\log_{10}$ IU/mL) and interferon-gamma inducible protein-10 levels (IP10>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

Hepatology. 2013;58. Abstract 915. Hepatol Int 2008;2(3):370; J Clin Virol. 2013 Apr;56(4):299.

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 ± HBIG and complete vaccine series
- High HBV DNA levels, typically observed in HBeAg positive women
  - ≥10% risk of transmission despite HBIG and vaccine prophylaxis
- Consider tenofovir therapy in 3rd 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

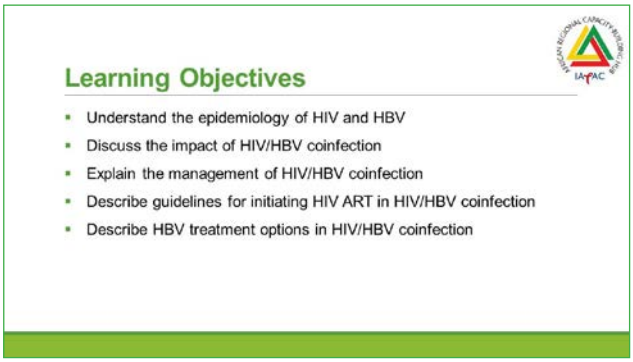
MANAGEMENT CONSIDERATIONS FOR HIV/HBV COINFECTION

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

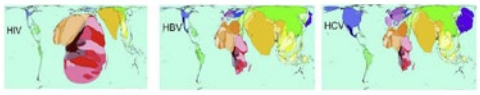
Supporting Materials:
PowerPoint Slides
Case Study (refer to Learning Activities section)



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/HCV Mortality (annual death rate) (www.worldmapper.org in Nov 2012)

Clinical Infectious Diseases 2012; 55(4):507; J Clin Virol 2014;61:20

HIV/HBV vs HIV/HCV Coinfection in Sub-Saharan Africa

- HIV/HBV coinfections tend to outnumber HIV/HCV coinfections
  - chronic HBV coinfection reported in 36% 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 coinfection**

Clinical Infectious Diseases 2012; 55(4):507; J Clin Virol 2014;61:20

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

Bull Soc Pathol Exot 2009;102:226; J Clin Virol 2014;61:20

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 peri-partum period
- Maternal HIV infection increases mother-to-child transmission of HBV (2.5-fold in one West African study) → HIV promoting HBV replication

Bull Soc Pathol Exot 2009;102:226; J Clin Virol 2014;61:20

Impact of HIV/HBV Coinfection

HIV COINFECTION PROMOTES:

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

AIDS 2005;19(6):593; J Acquir Immune Defic Syndr 2009;24(3):211; J Int Dis 2013;208(9):1454; South Afr Med J 2012; 102:157; World J Hepatol 2015; 2: 95-73; AIDS 2011; 25: 1727; Antivir Ther 2011;16:401; South Afr Gastroenterol Rev 2004; 2(3-14; South Afr J Epidemiol Infect 2008; 23(1): 14; Lancet 2002; 360(9341):1921

Impact of HIV/HBV Coinfection (continued)

- CD4 count <200 cells/mm^3 is associated with 16.2 fold increase in risk of liver-related death compared to CD4 count >350 cells/mm^3
- 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 - 4 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

- Triple HIV/HBV/HCV – Treat the dominant virus

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013; Int J STD AIDS 2013;24(2):117

Management of HIV/HBV Coinfection (continued)

Aetiology of abnormal liver profile: often multifactorial

- Drug-induced liver injuries
  - HIV ART, TB drugs, cotrimoxazole, fluconazole, traditional, herbal/alternative supplements
- HIV related opportunistic infections
- HBV clearance
- Emergence of drug resistance
- IRIS
- Reactivation after withdrawal of therapy
- Super-infection with HCV, HAV, HDV, and HEV
- Comorbidities - Non-alcoholic fatty liver disease, alcoholic liver disease

Management of HIV/HBV Coinfection (continued)

- Deranged liver enzymes often multifactorial
- More aggressive natural history of HBV and possibility of comorbidities

Lower threshold for performing liver biopsy to assess the differential diagnosis and the stage and grade of histologic injury

- Noninvasive methods - serum biomarkers and transient elastography to assess fibrosis

J Infect Dis. 2002;186:23-31; Lancet 2002;360:1921-1926; J Hepatol 2006;56:1074-1083

Initiation of HIV ART in HBV Coinfection

2013 WHO ARV guidelines recommend initiation of HIV ART in

- All HIV-infected adults with a CD4 cell count <500 cells/mm^3
  - 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 cirrhotics
- All pregnant or breastfeeding women regardless of CD4 count
- All children less than 5 years of age regardless of CD4 count

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.

Initiation of HIV ART in HBV Coinfection (continued)

Goal of therapy

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

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

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

Hepatology 2006;31:1030-1031; Lancet 2001;358:718-723; J Hepatol 2012;31:167-185 (EASL); Hepatol 2009;50:661 (AASLD); AIDS 2013;27(14):2219

Treatment of HIV/HBV Coinfection

Fixed-dosed combination (tenofovir, lamivudine/emtricitabine and efavirenz)

HBeAg-positive patients after 5 years of treatment: high rates of

- HBV DNA suppression (90%)
- HBeAg loss (46%)
- HBsAg loss (12%)
- No evidence of resistance
- Reduced progression to cirrhosis
- Risk of HCC persists, but is low
- No significant difference in response rates compared with HBV monoinfection

Gastro 2010;139(6):1934; AIDS 2013;27(14):2219

HIV/HBV Coinfection Treatment Options

Monitoring on FDC

- Recommended annual renal function assessment
- Consider annual assessment of bone function

Renal impairment

- Adjust tenofovir dose according to GFR

Tenofovir contraindicated (HIV nephropathy)

- Little data on the best alternative treatment
- Consider entecavir as part of HIV ART regimen
  - not alone; has weak HIV antiviral activity
  - no previous exposure to lamivudine
  - previous lamivudine, but no evidence of lamivudine associated HBV polymerase resistance

HIV/HBV Coinfection Treatment Options (continued)

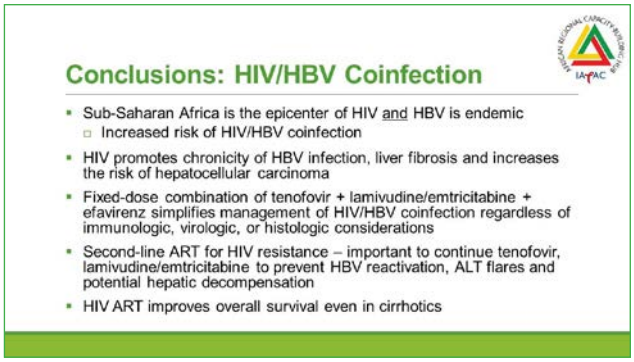
- Treatment of HIV without the use of tenofovir in the regimen
  - may lead to flares of hepatitis B due to ART-associated IRIS
- Treatment discontinuation, especially lamivudine, associated with
  - HBV reactivation, ALT flares, and hepatic decompensation
- If ARVs need to be changed because of HIV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

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013

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/emtricitabine + efavirenz simplifies management of HIV/HBV coinfection regardless of immunologic, virologic, or histologic considerations
Second-line ART for HIV resistance – important to continue tenofovir, lamivudine/emtricitabine to prevent HBV reactivation, ALT flares 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

Ultrasound liver: Liver normal size and normal echogenicity with smooth contours. No biliary dilatation. Portal vein patent with normal hepatopetal flow. Normal spleen.

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 is 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 decompensated 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.

FURTHER INVESTIGATIONS

FBC: Hb 12.5 g/dl, WCC 4.2 and platelets 158 x109/l

Creatinine: 90 umol/l (49-90) eGFR 98 ml/min/1.73m2

Liver profile: Total bilirubin 19 umol/l (0-21), conjugated bilirubin 10 umol/l (0-6), ALT 31 units/l (5-40), AST 35 units/l (5-40), ALP 116 units/l (40-120), GGT 32 units/l (0-35), albumin 37 g/l (35-52)

HBsAg positive, HBeAg negative, HBeAb positive

HBV DNA: 9 678 IU/ml.

Alpha-fetoprotein: 4.6 ug/l (0-7) eGFR 98ml/min/1.73m2

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 x109/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)

Ultrasound liver: Liver normal size and normal echogenicity with smooth contours. No focal lesions. No biliary dilatation. Portal vein patent with normal hepatopetal flow. Normal spleen.

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?

MODULE 6: MANAGEMENT OF HIV/HBV COINFECTION

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/mm^3.

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 66units/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 x109 /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-adherance) 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 HBIg (protective antibody called immunoglobulin) at birth to the baby; and
- Administering HBIg 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).

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