CAPACITY STRENGTHENING TOOLKIT

International Hepatitis C in Primary Care and Drug and Alcohol Settings Education Program

Supporting increased hepatitis C screening, linkage-to-care and treatment among people who inject drugs in South Africa

Contents

About

This toolkit is provided to participants of the INHSU Hepatitis C in Primary Care and Drug and Alcohol Settings Education Program. The toolkit is intended to provide participants with practical tools with which to implement HCV testing, linkage to care and treatment processes in their setting.

The toolkit is tailored in line with local guidelines and referral pathways for each workshop location.

Although some resources will be applicable only for participants working within the local area of workshop delivery, many, such as DAA treatment regimen quick reference guides, management procedure templates and assessment checklists, will be relevant regardless of practice location.

Resources applicable across all locations within South Africa are available as an enduring education program component as free downloads via the INHSU website:
INHSU - South Africa - HCV education program for health practitioners

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INHSU HCV in Primary Care and Drug and Alcohol Settings

Glossary

Term	Definition
APRI	AST-to-Platelet Ratio Index
Ascites	The accumulation of fluid (usually serous fluid which is a pale yellow and clear fluid) that accumulates in the abdominal cavity
Asymptomatic	Of a condition or a person producing or showing no symptoms
Cessation	The fact or process of ending or being brought to an end
Cerebral infarction	An area of necrotic tissue in the brain resulting from a blockage or narrowing in arteries supplying blood and oxygen to the brain
Cirrhosis	A complication of liver disease which involves loss of liver cells and irreversible scarring of the liver
Enzyme	Macromolecular biological catalysts. They accelerate chemical enzymes
Ethinylestradiol	An orally active estrogen and a synthetic derivative of estradiol, a steroid hormone and the major endogenous estrogen in humans
Etiology	The cause, set of causes, or manner of causation of a disease or condition
Fibrosis	The formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. This can be reactive, benign, or pathological state. In response to injury, this is called scarring, and if it arises from a single cell line this is called a fibroma.
Genotype	The genetic constitution of an individual organism
Hepatocellular carcinoma (HCC)	The most common type of primary liver cancer. It occurs predominantly in patients with underlying chronic liver disease and cirrhosis.
Jaundice	A medical condition with yellowing of the skin or whites of the eyes, arising from excess of the pigment bilirubin and typically caused by obstruction of the bile duct, by liver disease, or by excessive breakdown of red blood cells
Lethargy	A lack of energy
Myalgia	Pain in a muscle or group of muscles
Opioid	An opium-like compound that binds to one or more of the three opioid receptors of the body
Opioid agonist treatment	An effective treatment for addiction to opioid drugs such as heroin and involves taking the opioid agonists methadone or buprenorphine (suboxone)
Palmar erythema	Reddening of the palms
PCR	Polymerase Chain Reaction
Peripheral edema	An accumulation of fluid causing swelling in tissues perfused by the peripheral vascular system, usually in the lower limbs

Portal hypertension	An increase in the blood pressure within a system of veins called the portal venous system
RNA	Ribonucleic acid
Serology	The scientific study or diagnostic examination of blood serum, especially with regard to the response of the immune system to pathogens or introduced substances
Spider nevi	A collection of small, dilated blood vessels that are clustered close to the skin's surface
Thrombocytopenia	A condition in which you have a low blood platelet count
Viremic	A medical condition where viruses enter the blood stream and hence have access to the rest of the body

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HCV

1 When To Test

Clinical Indicators

- Abnormal liver function tests (LFTs) (adults, ALT <40 U/L)
- Jaundice

Presence of Risk Factors

- Injecting drug use (current/ever)
- Sharing of drug use equipment
- Born in high prevalence region^
- Blood transfusions, blood products, organ transplant and traditional practices before 1992 in South Africa
- Unsterile tattooing/body piercing
- Unsterile medical/dental procedures/blood transfusions in high prevalence countries
- Time in prison
- Needlestick injury
- Mother to child transmission
- Sexual transmission in men who have sex with men (MSM)
- Sexual transmission in those who are HIV positive
- Receiving haemodialysis

^Africa, the Middle East (in particular Egypt), the Mediterranean, Eastern Europe, and South Asia

Other

- Initiating PrEP
- When someone requests a test

When gaining informed consent before testing, discuss:

- Reason for test
- What a positive antibody result means
- Next steps if antibody positive
- Availability of curative treatment

2 Test/s, Results and Actions

Request HCV Antibody (Ab)*

HCV Ab negative

HCV Ab positive

HCV RNA (quantitative/qualitative) **+ LFTs**

HCV RNA negative

HCV RNA positive

Does NOT have HCV

Has CLEARED HCV

Has CURRENT HCV

NO action
However, if possible recent infection re-test (HCV Ab), or if ongoing risk factors repeat screening (HCV Ab) annually

RE-TEST if:
Ongoing risk factors
(repeat RNA test annually)

Further ASSESSMENT and TREATMENT
(see next page)

When conveying a NEGATIVE result, discuss:

- Modes of transmission
- Strategies for reducing risk

When conveying a POSITIVE result, discuss:

- Availability of curative treatment
- Modes of transmission and risk reduction
- Lifestyle factors e.g. alcohol minimization, diet
- Availability of peer support, information and any other support services

This resource was originally developed by ASHM. It has been adapted for South Africa by ASHM and the International Network on Health and Hepatitis in Substance Users (INHSU), in partnership with local partners.

***If high level suspicion also consider requesting reflexive HCV RNA + LFTs**

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HCV

3 Pre-Treatment Assessment

Baseline screening after positive HCV PCR

- ☐ Complete Blood Count (CBC)
- ☐ Urea, electrolytes, creatinine
- ☐ AST, ALT, GGT, ALP, Tbil, Dbil, INR, Alb

Assess liver fibrosis: cirrhotic status

- ☐ Signs of chronic liver disease (spider naevi, palmar erythema, jaundice, encephalopathy, hepatomegaly, splenomegaly, ascites, peripheral oedema)
- ☐ Non-invasive assessment of fibrosis:
  - Serum biomarkers such as FIB-4 or APRI (<1.0 means cirrhosis unlikely). Calculator available. hepatitisc.uw.edu/page/clinical-calculators/apri
  - Elastography assessment e.g. FibroScan® (>12.5 kPa consistent with cirrhosis)
  - Ultrasound assessment

Check for other causes of liver disease

- ☐ Check for viral coinfection:
  - HIV Ab
  - Hepatitis A – check hep A IgG; vaccinate if negative
  - Hepatitis B – check HBsAg, anti-HBc and anti-HBs; vaccinate if all negative
- ☐ Heavy alcohol intake
- ☐ Fatty liver disease - check weight, BMI

Check for other major co-morbidities

- ☐ Renal impairment (eGFR < 50)

Review previous HCV treatment

- Choice/length of treatment may be influenced by prior HCV treatment experience/response

Consider pregnancy and contraception

- HCV treatment not recommended for use in pregnant or lactating women

4 Treatment

Is your patient likely to have cirrhosis?
(APRI > 2 or FibroScan® > 12.5)

☐ Yes

Consider discussion with, or referral to experienced HCV treater

☐ No

Has your patient received previous treatment for HCV?

☐ Yes

Consider discussion with, or referral to experienced HCV treater

☐ No

Treatment	Dosage	Duration if no cirrhosis present
SOF/VEL~ (Epclusa®)	400/100 mg Once-daily (1 pill, +/- food)	12 weeks
SOF/DCV~	400/60 mg Once-daily (1 pill + food)	12 weeks
SOF/LDV~ (Harvoni®)	400/90 mg Once-daily (1 pill +/- food)	8 - 12 weeks

- ☐ Check South Africa Guidelines for further information
- ☐ Check for drug-drug interactions at hep-druginteractions.org
- ☐ Consult your provincial drug plan for coverage

~SOF/VEL = Sofosbuvir/Velpatasvir"
~SOF/DCV = Sofosbuvir/Daclatasvir" – requires section 21 application
~SOF/LDV = Sofosbuvir/Ledapasvir" – genotype 1a, 1b, 4 (but not subtype 4r) & 5 only

5 Monitoring

Monitoring while on treatment

- Generally not required, but approach should be individualized
- Side effects of HCV treatment are generally minimal
- Consider monitoring adherence

12 weeks post treatment

- ☐ HCV RNA to confirm cure (sustained virological response SVR12 = cure)
- ☐ Liver enzymes

6 Follow Up

If your patient has:

No cirrhosis and normal liver enzyme results (adults, ALT< 40 U/L)
No clinical follow-up for HCV required

Ongoing risk factors
Annual HCV RNA test. If re-infected offer re-treatment. Offer education on harm reduction strategies

Abnormal liver enzyme results
(adults ALT <40 U/L) Evaluate for other causes of liver disease and refer to specialist for review

Cirrhosis
Refer to specialist. Patients with cirrhosis require long-term monitoring:

- 6-monthly abdominal ultrasound (hepatocellular carcinoma screening)
- Consideration of screening for esophageal varices

CONSULT WITH A SPECIALIST IF:

Pre-treatment

- Cirrhosis is present or likely – APRI ≥2 and elastography score not available; elastography >12.5kPa
- Coinfected with HIV or HBV
- Renal impairment (eGFR < 50)
- Prior treatment failure of HCV treatment
- Complex drug interactions
- Complex co-morbidities
- Not comfortable prescribing HCV treatment

During treatment

- Major medication side effects

Post treatment

- RNA positive 12 weeks post treatment
- Abnormal liver enzymes at SVR12

Disclaimer: Guidance provided on this resource is based on best-practice at the time of publication. This quick-reference guide is not intended to be a comprehensive list of all available options.

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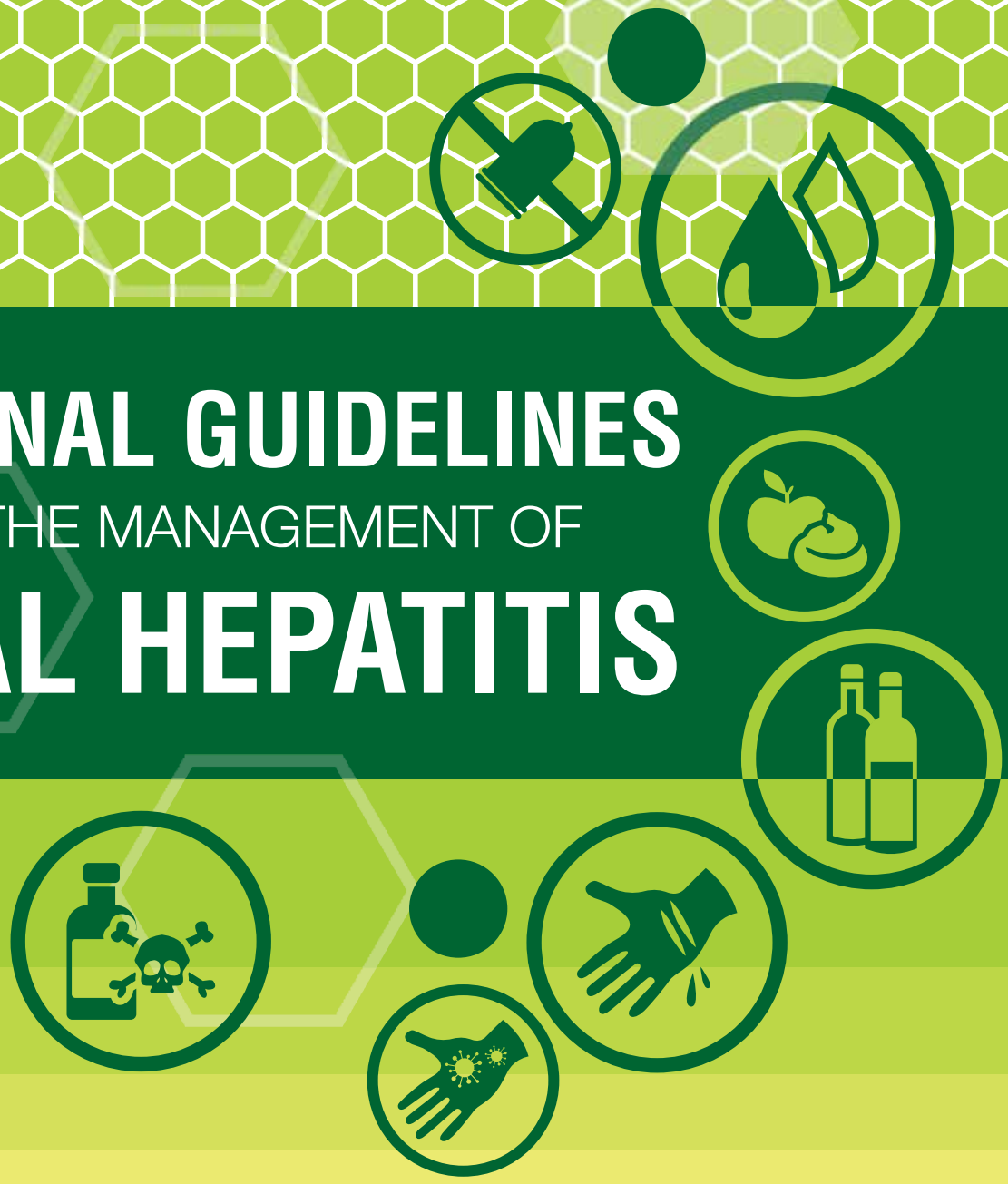
NATIONAL GUIDELINES
FOR THE MANAGEMENT OF
VIRAL HEPATITIS



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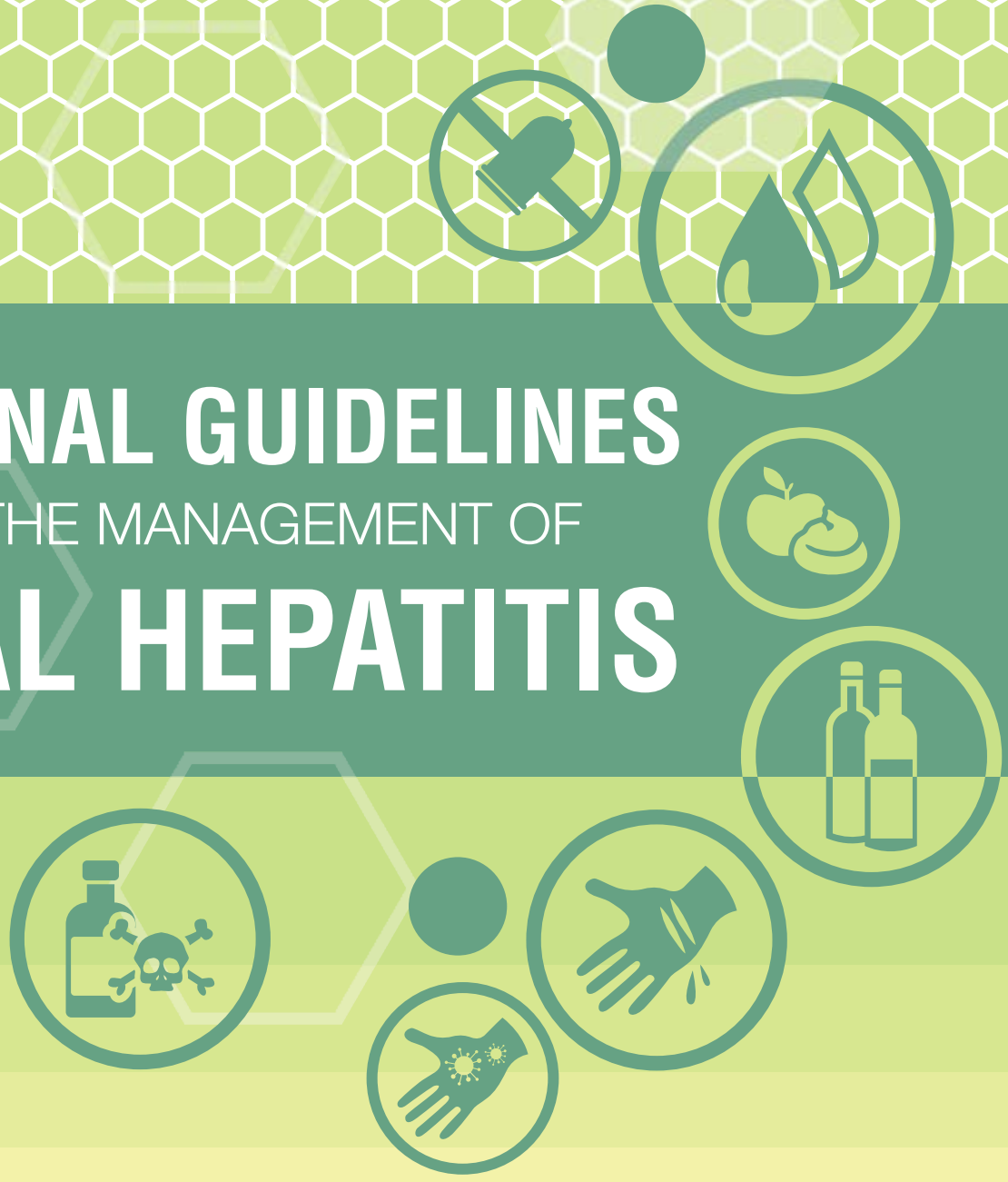
2030 NDP

NATIONAL GUIDELINES
FOR THE MANAGEMENT OF
VIRAL HEPATITIS




Hepatitis

FOREWORD

It is my pleasure to present the first National Guidelines for the Management of Viral Hepatitis. Viral hepatitis is defined as inflammation of the liver cells due to viral infection. The burden of liver disease in South Africa is mostly underestimated as viral hepatitis, in particular chronic infection, is a silent and neglected cause of morbidity and mortality. However, the burden of disease is likely substantial given the prevalence of chronic viral hepatitis. This burden is further compounded by the lack of screening and access to care and treatment as well as inadequate disease surveillance, human and financial resources.

According to the most recent estimates of the Global Burden of Disease Study, viral hepatitis is responsible for approximately 1.5 million deaths each year, which is comparable to the annual deaths from AIDS (1.3 million), malaria (0.9 million) and tuberculosis (1.3 million). Mortality due to viral hepatitis has increased since 1990 and it is now the seventh leading cause of mortality in the world.

Hepatitis A (HAV) and B (HBV) are highly endemic in South Africa, but there is limited data on hepatitis C, D and E. However, sporadic cases of hepatitis E have been reported as a result of travel to high-risk areas outside South Africa. South Africa has one of the largest HBV burdens globally with an estimated hepatitis B surface antigen (HBsAg) prevalence of 6.7 per cent (3.4 million individuals). Hepatitis C is mainly a concentrated epidemic amongst key populations. Recent studies have demonstrated that the prevalence of hepatitis C is as high as 93 per cent among people who inject drugs (PWID) in Pretoria. If left untreated, around one third of those chronically infected with viral hepatitis will die as a result of serious liver disease, including cirrhosis, liver failure and hepatocellular carcinoma.

It is the role of the Department of Health to decrease morbidity and mortality due to emerging and re-emerging epidemic-prone infectious diseases. Therefore, these guidelines were developed, with the purpose to:

- inform healthcare workers in the public and private sectors about the disease, its epidemiology in South Africa and current methods of diagnosis and therapy
- strengthen the healthcare response to viral hepatitis
- empower communicable diseases workers and stakeholders to make informed decisions regarding appropriate and cost effective interventions

I trust these guidelines will assist health workers by providing information on the disease and prevention and control measures.

Dr ZL Mkhize, MP
Minister of Health
Date: December 2019

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N Ramalwa: Limpopo Department of Health

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LIST OF ACRONYMS

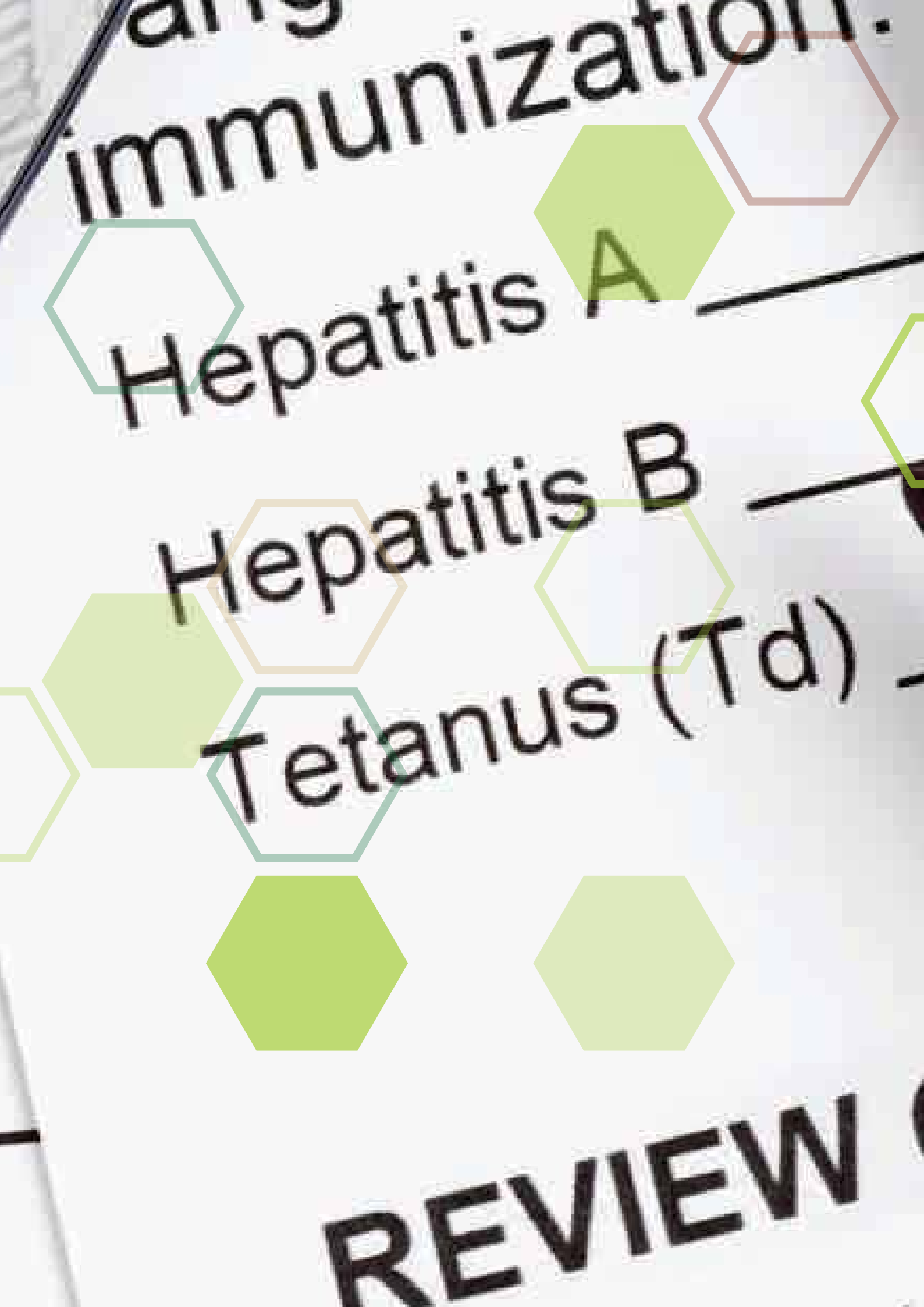
AIDS	Acquired immunodeficiency syndrome
AFP	Alpha-fetoprotein
APRI	AST to Platelet Ratio Index
ALP	Alkaline phosphatase
ALT	Alanine aminotransaminase
anti-HAV IgM	Hepatitis A IgM antibody
anti-HAV IgG	Hepatitis A IgG antibody
anti-HBe	Hepatitis B e antibody
anti-HBs	Hepatitis B surface antibody
anti-HBc total	Total Hepatitis B core antibody
anti-HCV	Hepatitis C antibody
anti-HDV IgG	Hepatitis D IgG antibody
anti-HDV IgM	Hepatitis D IgM antibody
anti-HEV IgG	Hepatitis E IgG antibody
anti-HEV IgM	Hepatitis E IgM antibody
APRI	AST to platelet ratio index
ART	Antiretroviral therapy
AST	Aspartate aminotransaminase
BCG	Bacillus Calmette-Guérin (or Bacille Calmette-Guérin)
cccDN	covalently closed circular DNA
CCMT	Comprehensive HIV and AIDS care, management and treatment
CDC	Centers of Disease Control and Prevention, Atlanta, United States of America (USA)
CHB	Chronic hepatitis B
DAA	Direct acting antivirals
DALY	Disability adjusted life years
DNA	Deoxyribonucleic acid
DM	Diabetes mellitus
ds	double stranded
DSV	Dasabuvir
DTP	A triple vaccine against diphtheria, tetanus, and pertussis
EIA	Enzyme immunoassay
ELISA	Enzyme linked immuno-sorbent assay
EOT	End-of-treatment response
EPI	Expanded Programme on Immunisation
EPP	Exposure-prone procedures
EVR	Early virological response
FBC	Full blood count
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase

LIST OF ACRONYMS [CONTINUED]

GT	Genotype
HAART	Highly active antiretroviral therapy
HAS	HIV, AIDS and STIs
HAV	Hepatitis A virus
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
HBeAb	Hepatitis B e antibody
HBcAg	Hepatitis B core antigen
HBcAb	Hepatitis B core antibody
HBcIgM	Hepatitis B core IgM antibody
HBIG	Hepatitis B immunoglobulin
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCWs	Healthcare workers
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIB	Haemophilus influenzae type B
HIV	Human immunodeficiency virus
IFN	Interferon
IFG	Impaired fasting glucose
IgG anti-HBc	Hepatitis B IgG core antibody
IgM anti-HBc	Hepatitis B IgM core antibody
INR	International normalised ratio
IPV	Intramuscular Polio Vaccine
IRIS	Immune reconstitution inflamatory syndrome
IU/mL	International units per millilitre
IVI	Intravenous injection
KZN	Kwa-Zulu Natal
LFT	Liver function test
MDG	Millennium Development Goal
mRNA	messenger RNA
MSDS	Material safety data sheet
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
NASTAD	National Alliance of State and Territorial AIDS Directors
NAT	Nucleic acid testing
NBI	National Bioproducts Institute

LIST OF ACRONYMS [CONTINUED]

NHLS	National Health Laboratory Services
NICD	National Institute for Communicable Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NITs	Non-invasive tests
NMC	Notifiable medical condition
NUC	Nucleostide analogue
OMB	Ombitasvir
OPV	Oral polio vaccine
PEP	Post-exposure prophylaxis
PCR	Polymerase chain reaction
PrEP	Pre-exposure prophylaxis
RT-PCR	Reverse transcription-polymerase chain reaction
PEG	Polyethylene glycol
PI	Protease inhibitors
PMTCT	Prevention of mother-to-child transmission
PPV	Positive predictive value
PTV	Paritaprevir
PWID	People who inject drugs
RAS	Resistance associated substitutions
RNA	Ribonucleic acid
RSA	Republic of South Africa
RTV	Ritonavir
RVR	Rapid virological response
SAHPRA	South African Health Products Regulatory Authority
SANBS	South African National Blood Service
SVR	Sustained virological response
TAF	Tenofovir Alafenamide
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VCTE	Vibration controlled transient elastography
WHA	World Health Assembly
WHO	World Health Organization
YMDD	Tyrosine-methionine-aspartate-aspartate


immunization.
Hepatitis A
Hepatitis B
Tetanus (Td)
REVIEW

INTRODUCTION

CHAPTER 1

Hepatitis is a general term referring to an inflammation of the liver. It occurs as a result of infection with various pathogens; exposure to alcohol, medications, chemicals and toxins; and autoimmune disorders. There are five types of hepatotrophic viruses: Hepatitis A, B, C, D and E (HAV, HBV, HCV, HDV and HEV), named according to the order in which they were discovered. In the 1960s, only two types were known (A and B), but by the late 1970s and beyond, new viruses (C and E) were discovered. Hepatitis viruses are either ribonucleic acid (RNA) (hepatitis A, C, D and E), or deoxyribonucleic acid (DNA) viruses (hepatitis B). The five hepatotrophic viruses are broadly classified into two groups namely, enteric and parenteral (Table 1).

Table 1: Hepatotrophic viral classification

Hepatotrophic-viral type	Genetic make up		Classification group
	RNA	DNA	Enteric/parenteral
HAV	✓	...	Enteric
HBV	…	✓	Parenteral
HCV	✓	...	Parenteral
HDV	✓	...	Parenteral
HEV	✓	...	Enteric

Key: ✓ = yes; ... = no

The enteric viruses, HAV and HEV, are transmitted primarily via the faecal-oral route and may be associated with outbreaks of acute illness. Infections frequently occur following ingestion of contaminated food and/or water. Clinical presentations range from asymptomatic to mild or severe disease, but are usually self-limiting with no long-term sequelae. The notable exception is the unusually high mortality caused by the HEV in pregnant women, up to 25 per cent. Measures to improve personal and environmental hygiene are adequate to prevent the spread of these enteric hepatitis viruses.

The parenterally transmitted viruses (B, C and D) are primarily transmitted via exposure to infected blood and body fluids. Common routes of transmission include mother-to-child transmission (MTCT), sexual transmission, blood/blood product transfusions and percutaneous exposure (needle-stick injuries, body piercing/traditional scarification, unsafe injection practices and inadequately sterilised medical equipment). Clinical presentations include acute hepatitis as well as chronic infection leading to the complications of cirrhosis, liver failure and hepatocellular carcinoma.

The clinical symptoms and signs of the different viruses are often indistinguishable, with the epidemiology being markedly different.

Currently effective and licensed vaccines are available for the prevention of HAV, HBV and HEV. Furthermore, HDV can be prevented as HBV immunisation is protective against HDV.

These guidelines have been developed to improve the management of viral hepatitis in South Africa and to enable healthcare workers to implement the WHO goal of eliminating viral hepatitis by 2030[1,2].

IMPORTANT:
VIRAL HEPATITIS IS A NOTIFIABLE MEDICAL CONDITION (NMC)

EPIDEMIOLOGY OF VIRAL HEPATITIS

CHAPTER 2

GLOBAL PICTURE

Viral hepatitis is a group of infectious diseases that represent a significant global health challenge. According to the most recent estimates of the *Global Burden of Disease Study*[1], viral hepatitis is responsible for approximately 1.45 million deaths each year, which is comparable to the annual deaths from HIV and AIDS (1.3 million), malaria (0.9 million) and tuberculosis (1.3 million). Mortality due to viral hepatitis has increased by 63 per cent since 1990 and it is now the seventh leading cause of mortality in the world, yet there has been a persistent lack of global awareness of the severity of the problem as well as a lack of commitment to combat the disease[2-6].

An estimated 257 million individuals are chronically infected with HBV, and 71 million with HCV. Globally, most of the morbidity and mortality is caused by HBV and HCV infections: 96 per cent [95 per cent CI 94–97] of mortality and 91 per cent [88–93] of disability adjusted life years (DALYs) in 2013[6]. It is estimated that 95 per cent of individuals with chronic HBV and/or HCV are unaware of their infection and do not benefit from clinical care, treatment and interventions designed to reduce onward transmission. Without appropriate diagnosis and treatment, around one third of those chronically infected with viral hepatitis will die as a result of serious liver disease, including cirrhosis, liver failure and hepatocellular carcinoma [4-6].

SOUTH AFRICAN CONTEXT

The burden of liver disease in South Africa is mostly underestimated. Viral hepatitis, in particular chronic infection, is a silent and neglected cause of morbidity and mortality. The burden of disease is likely to be substantial given the prevalence of chronic viral hepatitis, especially HBV. This burden is further compounded by the lack of screening, access to care and treatment, as well as inadequate disease surveillance, human and financial resources.

Despite the availability of HAV and HBV vaccines, effective therapy for HBV, and now a potential cure for HCV with the new direct acting antivirals (DAAs), viral hepatitis remains an important cause of morbidity and mortality in South Africa. Co-infection with HIV further exacerbates the burden of liver disease.

In summary, studies conducted in South Africa, mainly on HBV and HCV, have produced varying seroprevalence estimates. National estimates for each hepatotrophic virus remains a significant challenge. This is because the studies were conducted in different population groups (having increased or

lower risk probability), utilised different sample sizes and used different laboratory screening methods, some with and others without confirmatory testing, to arrive at seroprevalence estimations. In addition, the studies have a wide geographical distribution.

Recent national data from different sources may also be utilised to generate more current seroprevalence estimates, such as from antenatal clinic surveillance studies or blood banks. Having recent information can provide more concrete evidence-based input for policy making on prevention and care of viral hepatitis in South Africa.

2.1 Epidemiology of Enteric Hepatitis Viruses

HAV

Globally, HAV affects 1.4 million people annually. In many regions of South Africa, the incidence of HAV is strongly correlated with poor socioeconomic conditions and limited access to safe water and inadequate sanitation contributing to the endemic nature of the disease where up to 80 per cent of children are anti-HAV IgG-positive by between 11 and 13 years[7-9].

With environmental stability being the seventh Millennium Development Goal (MDG) to be achieved by 2015, 64 per cent of those in sub-Saharan Africa now have access to an improved drinking water source[5]. In South Africa, although access to safe water and sanitation has improved, significant numbers of people are still reliant on unimproved, potentially faecally contaminated water.

There is a highly effective HAV vaccine available that imparts long-term immunity. This HAV vaccine is not part of South Africa's Expanded Programme on Immunisation (EPI) since HAV is usually a self-limiting subclinical illness in young children in endemic regions. However, there are no recent South African seroprevalence studies and with changing socioeconomic demographics as well as more integrated societies in South Africa, the epidemiology of HAV may be in transition towards a lower HAV endemnicity level and a potential increase in symptomatic infections.

HEV

Global infections of HEV are estimated to reach around 20 million cases annually. Documented seroprevalence rates in South Africa range between two and 29 per cent, suggesting that HEV is endemic in South Africa[10]. However, no epidemics have occurred in South Africa. HEV is enterally transmitted via faecal-oral (Genotypes 1 and 2) and zoonotic (Genotypes 3 and 4) routes of transmission. Ensuring access to safe water and food supplies and adequate sanitation is important to prevent outbreaks related to HEV Genotype 1 and 2 infections.

2.2 Epidemiology of Parenteral Hepatitis Viruses

HBV

The global burden of HBV is significant and it is estimated that one third of the world's population (about two billion people) have been infected with HBV at some point in their lives; and of these 257 million people are chronically infected6. One million people die annually from HBV and its associated complications. HBV is endemic in South Africa, resulting in a significant burden of clinical disease as a result of the progression to cirrhosis and the development of the complications of liver failure or hepatocellular carcinoma. There is a 15 to 25 per cent risk of dying from HBV-related liver diseases[11].

HBsAg seroprevalence varies geographically between two and 20 per cent with Asia, sub-Saharan Africa, Southern Europe and Latin America having the highest seroprevalence rates. The estimated HBsAg prevalence in South Africa prior to universal HBV immunisation (administered at 6, 10 and 14 weeks) ranged between 0.2 and 9.6 per cent with evidence of HBV past exposure (HBsAg-negative, anti-HB IgG core positive) between five and 76 per cent. Seroprevalences differed between genders, ethnic groups and between rural and urban areas [12-14].

In a recent systematic review based on observational studies performed in the general population amongst blood donors, healthcare workers and pregnant women between 1965 and 2013, South Africa had an estimated 6.7 per cent HBsAg seroprevalence, i.e. high intermediate endemicity with an estimated 3 445 477 individuals infected with HBV based on 18 studies and 136 356 participants[15].

South Africa has not introduced compulsory maternal HBsAg screening nor an HBV birth dose vaccine and has had no catch-up HBV immunisation programme (e.g.Taiwan HBV immunisation programme). The aggressive HBV immunisation programme proved exemplary in Taiwan, where universal immunisation, introduced in 1984, together with a catch-up immunisation programme and improved maternal screening, resulted in a decrease in the prevalence of HBsAg-positivity in children aged younger than 15 years from 9.8 per cent in 1984 to 0.7 per cent in 1999[16,17]. Furthermore, the prevalence of hepatocellular carcinoma (HCC) in children aged between six and nine years in Taiwan decreased from 5.2 cases per million population in 1984 to 1.3 per million in the first immunisation cohort[18,19]. Apart from healthcare workers, there has been no targeted immunisation of high-risk groups in South Africa.

Despite the documented success of the introduction of HBV immunisation into the EPI in April 1995, with overall seroprevalence of HBsAg declining from 12.8 per cent to three per cent in some studies in the pre-HIV era 20-24, recent studies have shown that HBsAg prevalence in adults ranges from three to 25 per cent. The highest rates are documented in HIV-infected adults 25-30. HIV/HBV co-infection also increases the potential risk of perinatal HBV transmission and is associated with a more aggressive natural history of chronic HBV[31]. A recent key population surveillance study (sample of 3 500 individuals) in people who inject drugs, men who have sex with men (MSM) and sex workers conducted in seven cities in South Africa showed an average of four per cent HBsAg-positivity[32].

A retrospective seroprevalence study from Kwazulu-Natal in infants younger than 18 months revealed a 10 per cent overall HBV seroprevalence: 13 per cent (21/161) in HIV-positive infants compared to 7.5 per cent (12/161) in HIV-negative infants despite universal HBV immunisation[33].

HBV endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged between five and nine years and adults[34]. In South Africa, in order to eliminate HBV, which is an entirely vaccine-preventable disease, it is essential to prevent the neonatal and early childhood acquisition. This requires the introduction of the maternal HBsAg screening, consideration of Tenofovir in the third trimester of pregnancy to prevent MTCT, administration of HBV birth dose vaccine as recommended by the WHO and the immunisation of high-risk adults[46].

HCV

Globally, an estimated 71 million people are infected with HCV[5]. Most HCV infections are in North and West Africa; and East and Central Asia. Each year, approximately 704 000 people die from HCV-related liver diseases. HCV is parenterally transmitted with the well-recognised modes of HCV transmission typically being prior (usually pre-1992) blood and blood product exposure or injecting drug use. Other modes of transmission have included percutaneous exposure via unsafe injection practices particularly amongPWID; inadequately sterilised medical equipment; needle stick injuries in healthcare workers, body piercings and traditional scarification; sexual transmission; and MTCT. HIV and HCV have common routes of transmission, and it is estimated that globally, 2.3 million persons are HIV/HCV co-infected with a prevalence notably higher in MSM and PWID.[36]

HCV seroprevalence and identifiable high-risk factors in South Africa are poorly understood and characterised. Previous data suggested a seroprevalence in urban blood donors of 0.01 to 2.6 per cent (low risk), with a higher rate in the rural population (3.8 per cent)[35] and recent studies confirm higher prevalences in high-risk key populations[37,38]. Recent studies have confirmed a high HCV burden among people who use drugs, including people who inject drugs. A 2016/2017 study among 3 500 high-risk key populations (sex workers, men who have sex with men, people who use/inject drugs) across seven South African cities identified an HCV viraemic prevalence of 13 per cent, highest among PWID (44 per cent n=939) ranging from 33 per cent in Durban to 69 per cent in Pretoria[32]. HCV prevalence among people who use drugs, but had not injected in the previous year was eight per cent (n=224)[32]. A subsequent bio-behavioural survey conducted in 2017 found HCV viraemiac prevalence of 63 per cent in Cape Town (n=348) and 93 per cent in Pretoria (n= 544) using respondent driven sampling methodology. Robust national population size estimates of PWID are lacking, but cited as between 67 000 and 75 000 39,40. A robust, multi-method assessments of PWID in 2017 estimated the number of PWID to be 4 500 in Pretoria and 1 500 in Cape Town (personal communication with Prof. Tim Lane).[41]

South Africa is a “pangenotypic” country with genotypes 1 to 5 occurring. Genotype 5a was first identified in South Africa and is a unique and prevalent genotype[42]. The most prevalent genotypes from the 2017 key population surveillance study (n=413) were type 1a (73 per cent) and 3a (15 per cent) and no

type 5 identified. With the advent of the new DAAs, sustained viralogical responses (SVR) of more than 90 per cent are now achievable for all genotypes and for almost all patient groups: Treatment naïve and experienced patients, cirrhotic patients, HIV/HCV co-infection and liver transplant recipients. An SVR equates with a cure and improves both liver-related and all-cause mortality in non-cirrhotic and cirrhotic patients. All HCV infected patients are now candidates for DAA treatment. Although, DAAs are not yet registered in South Africa, they are obtainable via a SAHPRA [former Medicines Control Council (MCC)] Section 21 application process for named patients. Registration is anticipated in 2019.

In order to eliminate HCV in South Africa, it will be essential to enhance seroprevalence surveillance and increase screening among high-risk groups, particularly PWID and provide easy, affordable, appropriate and accessible care for HCV-infected individuals.

HDV

HDV is a defective RNA virus that is dependent on HBV for its survival. In South Africa, seroprevalence rates are low, ranging from 0 to 0.6 per cent[43]. HDV co-infection should be considered in HBV-infected individuals, particularly from countries north of the equator where HDV seroprevalence is high44 and present with a clinical deterioration not due to HBV.

2.3 Rationale for The Consolidated Viral Hepatitis Guidelines

The 69th World Health Assembly (WHA) in May 2016 adopted the first viral hepatitis global health sector strategy for 2016 to 2021[45].The strategy addresses all five hepatitis viruses (A, B, C, D and E), with a particular focus on HBV and HCV, owing to the relative public health burden they represent. The strategy outlines a way ahead, and provides a vision of a world where viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable and effective care and treatment; a goal of eliminating viral hepatitis as a major public health threat by 2030; and targets that seek to reduce the incidence of hepatitis from the current six to 10 million new infections to 0.9 million infections by 2030, and to reduce the annual deaths from chronic viral hepatitis from 1.4 million to less than 0.5 million by 2030.

Achieving these targets will require a radical change in the hepatitis response, and will mean that hepatitis is elevated to a higher priority in public health responses aiming for a:

- 90 per cent reduction in new cases of chronic HBV and HCV by 2030
- 65 per cent reduction in HBV and HCV deaths by 2030
- 80 per cent of eligible persons with chronic HBV and HCV infections treated by 2030

2.4 Target Audience

These guidelines are aimed at equipping health workers working at primary, secondary and tertiary levels of care in the medical management of individuals with viral hepatitis in South Africa.

GUIDING PRINCIPLES

CHAPTER 3

3.1 Principles Guiding The Approach to Elimination of Viral Hepatitis1

The ultimate elimination of viral hepatitis requires an effective partnership between:

- affected communities
- professional, civil society and community-based organisations
- government
- researchers and health professionals

This partnership needs to be characterised by consultation, cooperative effort, respectful dialogue, resourcing and action to achieve the goal of the strategies.This includes leadership from the national Department of Health and the appropriate allocation of funds at both national and provincial level as well as the full cooperative efforts of all members of the partnership to implement agreed strategies of elimination.

These guidelines were developed to:

- inform healthcare workers in both the public and private sectors (at all levels of care) about the disease, its epidemiology in South Africa and the current methods of diagnosis and therapy
- strengthen the healthcare response to viral hepatitis
- empower communicable diseases workers and stakeholders to make informed decisions regarding appropriate and cost-effective interventions

3.2 Access to Care and Health Equity

Viral hepatitis is likely to have a disproportionate impact on certain groups within the South African society, including those with low socioeconomic status, those with poor access to healthcare, refugees and marginalised groups such as PWID, MSM, sex workers and inmates in correctional centres. In addition, co-morbidities such as HIV, TB and alcohol use are prevalent in South Africa and further add to the clinical burden of liver disease. In order to promote equity in health and to reduce the burden of disease among these groups, several human rights issues

such as stigma, discrimination, social exclusion and poor access to services need to be addressed from a social justice perspective.

It is important that efforts are undertaken to ensure that the relevant workforce in each setting understands the issues affecting at-risk populations, and how to effectively engage with and support them. All South Africans should have access to diagnosis, preventative measures and treatment for viral hepatitis. Finally, the design and provision of culturally appropriate information about viral hepatitis, and its prevention, treatment and care options are crucial to overcoming the barriers caused by poor health literacy in many settings within South Africa.

3.3 Health Systems Strengthening and Integration

A health system strengthening approach seeks to increase the capacities of individuals, systems and organisations that constitute the healthcare system. The national viral hepatitis plan will include a set of integrated and comprehensive actions to be implemented at a national level under defined objectives to be achieved within a specific time frame with an embedded monitoring and evaluation system. Of paramount importance is integration of disease-specific planning in national health sector planning, and integration of disease-specific services within the currently existing health services e.g. HIV clinics and a decentralised, community-based and largely preventative approach. This is the only way to maximise synergies, avoid duplication, achieve sustainability and promote cost-effectiveness.

The main areas to be addressed in the process of health systems strengthening are:

a) effective and transparent leadership and governance involving:

- strong political commitment, enabling national policy, leadership and accountability, a coordinated response towards the elimination of viral hepatitis
- decriminalisation and destigmatisation of key populations: PWID, MSM

b) fair and sustainable financing mechanisms addressing:

- implementation of diagnostic services, assessment of disease severity (AST to platelet ratio index [APRI] score, Fibroscan), prevention and treatment options for viral hepatitis
- equitable access to these services for those in need, but who cannot afford the required services

c) human resources for health

- an adequate number of appropriately trained workers to deliver high-quality, culturally competent interventions

d) essential medicinal products, infrastructure and technology

- sustained procurement and supply of cost-effective medicines, commodities and tools for prevention, diagnosis and treatment of viral hepatitis

e) service delivery

- delivery of comprehensive viral hepatitis interventions to those individuals that need them in all regions of South Africa, thereby ensuring appropriate linkage to care
- integration of community-based multipurpose healthcare facilities such as primary level healthcare centres, or through HIV/sexually transmitted infection clinics and antenatal services to improve access to care for patients with viral hepatitis
- focused responses towards populations and geographical areas with a disproportionate burden of diseases and risk for infection and onwards transmission e.g. PWID, MSM and prisoners

f) a functioning health information system for monitoring, evaluation and for informing decision-making

- timely analysis and dissemination of reliable information regarding changing epidemiology, potential epidemics, access to care and outcomes of viral hepatitis prevention and treatment strategies

HEPATITIS A (HAV)

CHAPTER 4

4.1 Introduction

HAV is the most common cause of acute viral hepatitis in many parts of the world, including South Africa. The virus is endemic in southern Africa, however the true burden of disease is unknown. Localised and more widespread community and institutional outbreaks occur in South Africa and frequently raise challenges for control, given limited resources. In addition, South Africa has a unique epidemiological pattern of disease with variations in rates of infection across different socioeconomic groups and provinces. In areas where socioeconomic standards are poor and there is inadequate access to clean water and sanitation, infection occurs early in life and produces mostly mild or asymptomatic disease. In these areas, rates of infection are higher, but morbidity considerably less and most people in such communities are immune by adolescence.

HAV characteristics:

- HAV is a picornavirus
- non-enveloped, single-stranded RNA virus
- only one serotype but can be grouped into four human genotypes (I, II, III, VII) using RNA sequencing[1-4].
- HAV persists in the environment for prolonged periods, but is inactivated by boiling (at more than 850C for one minute) and on exposure to household bleach (1:100 dilution in tap water)[3].

4.2 Transmission of Hav:

- faecal-oral transmission
  - o person-to-person spread
  - o anal-oral sexual transmission also occurs (MSM)
  - o ingestion of faecally contaminated food or water
- transmission via blood products has been described
- no evidence of transmission by saliva

4.3 Groups at Risk for Hav:

- people who are household/sexual contacts of infected individuals
- preschool children attending day care centres, their parents and siblings
- employees of day care centres

- volunteers working with children
- healthcare workers
- MSM
- residents and employees of closed communities (institutions): Personal hygiene of residents is compromised, residents are incontinent or wear nappies
- international travellers from non-endemic to endemic regions
- refugees residing in temporary camps following catastrophes or displacement
- individuals with chronic liver disease: Not at increased risk for infection, but are at risk for severe disease
- raw sewage workers
- food handlers: Not at higher risk for infection, but pose a high risk of transmission

4.4 Clinical Presentations of HAV

The incubation period for HAV is 15 to 50 days (average = 28 days). Individuals are most infectious two weeks prior to the onset of jaundice and infectivity then begins to fall, but most individuals will remain infectious for one to two weeks following the onset of jaundice[1]. However, prolonged shedding of the virus in stool has been documented, thus increasing the period of infectivity[6]. HAV infection is usually a self-limiting disease, there is no chronic carrier state and immunity following infection is considered to be life-long. The clinical presentation may vary and is influenced by factors such as age, changing socioeconomic demographics and the presence of underlying risk factors for severe disease[5,6].

Mortality rates:

- overall mortality: 0.3 per cent in icteric cases
- 0.1 per cent in those younger than 15 years
- increased mortality in older patients: One to two per cent in those older than 40 years

4.4.1 The different clinical presentations include:

a) asymptomatic infection

- most children younger than four years are completely asymptomatic

b) symptomatic hepatitis without jaundice

- children aged between four and six years: 90 per cent anicteric

c) symptomatic hepatitis with jaundice

- individuals older than 15 years, 40 to 70 per cent present with jaundice4
- prodromal illness precedes the jaundice in 85 per cent of individuals
  - loss of appetite, fatigue and malaise
  - flu-like symptoms: Fever, cough, coryza, pharyngitis, photophobia and headache
  - arthralgia and myalgia
  - nausea, vomiting and abdominal discomfort
  - diarrhoea
- prodromal symptoms usually decline with the onset of jaundice

d) rare extrahepatic presentations

- aplastic anaemia
- cutaneous necrotising vasculitis
- mononeuritis multiplex
- Guillane Barré Syndrome
- transverse myelitis

4.4.2 Complications of HAV

a) fulminant HAV

- rare complication
- more common in older adults and patients with chronic liver disease
- occurs during the first six to eight weeks of illness
- jaundiced, often nauseous and vomiting, develop hepatic encephalopathy and coagulopathhy and can rapidly progress to life-threatening cerebral oedema
- severity of the liver injury is often not appreciated in children younger than five years who present with acute HAV
  - jaundice is frequently the only initial clinical symptom
  - hepatic encephalopathy is often a late and terminal presentation
- mortality rates are 70 to 95 per cent
- almost 100 per cent mortality in individuals older than 50 years of age1,4

- liver transplantation: 65 per cent one year survival rates

b) relapsing HAV

- occurs in three to 20 per cent of patients
- four to 15 weeks after the initial symptoms have resolved
- characterised by relapse of symptoms and liver enzyme derangement
- positive anti-HAV IgM
- HAV is shed in the stool, rendering patients infectious
- increased risk in adults who return to work or strenuous exercise too early
- usually resolves within two to six months
- full recovery may take six to 12 months
- multiple relapses may occur over 12 months
- extra hepatic manifestations more common: Vasculitis, nephritis, arthritis
- no chronic carrier state1,4

c) cholestatic hepatitis

- persistent severe jaundice and associated pruritus
- minor elevation of transaminases
- synthetic function normal
- positive anti-HAV IgM
- biopsy: Centrilobular cholestasis
- jaundice may persist for three months or more
- full recovery over time1,4
- steroids should not be used to treat

4.5 Diagnosis of HAV

Viral hepatitis cannot be distinguished clinically or biochemically, but requires a serological diagnosis. Elevated transminases (the ALT and AST are usually 10 to100 times to the upper limit of normal) confirm the presence of hepatitis.

- acute HAV: Positive anti-HAV IgM
- previous exposure to HAV or post HAV-immunisation: Positive anti-HAV IgG

Most patients with acute HAV will have a positive anti-HAV IgG at initial presentation.

The latter will persist long term and provide lifelong immunity. Anti-HAV IgM levels will decline over three to six months following infection.

4.6 Prevention of HAV

4.6.1 General control measures to prevent faecal-oral transmission:[10,11]

- provide adequate water and sanitation
- promote good hand hygiene
- regularly inspect food establishments and compliance with safe food handling practices
- strictly adhere to standard infectious and contact precautions. This is usually sufficient to prevent the spread of infection in healthcare facilities and institutions

4.6.2 Specific control measures

Pooled intramuscular immuniglobulin (human normal immunoglobulin for intramuscular use - HNIG)

- pooled intramuscular HNIG provides passive immunity to HAV
- effective for both pre- and post-exposure prophylaxis when administered correctly
- pre-exposure prophylaxis: 0.02 ml/kg IMI (three months protection)or 0.06 ml/kg IMI four to six monthly for continued exposure
    - o recommended for travellers at high risk for severe disease and/or younger than two years or older than 40 years and departing in less than two weeks
- post-exposure prophylaxis: 0.02 to 0.04 ml/kg IMI, preferably within 72 hours of exposure
    - o can be administered up to 14 days post-exposure
    - o administration up to four weeks post-exposure may reduce disease severity in high-risk contacts and immunocompromised individuals

HAV vaccines

- effective for both pre- and post-exposure prophylaxis
- HAV vaccine is the method of choice for pre-exposure prophylaxis
    - o single dose with a booster at six to 12 months: 95 per cent efficacy after two doses

with at least 20 years protection, if not lifelong

- special considerations for HAV vaccine use:
  - pregnancy: single dose of HAV vaccine can be given
  - infants: HAV vaccine not licensed for use in children younger than one year
  - immunosuppressed individuals (including HIV positive and transplant patients)
    - inactivated vaccine and safe for use
    - responses to vaccine may be reduced in advanced immunosupression, including HIV
    - a third booster may need to be considered six to 12 months after the first dose
- in South Africa many adults are HAV immune and it will be cost effective to screen healthcare workers prior to HAV immunisation
- HAV immunisation can be given as soon as travel is considered (regardless of time to travel)
  - healthy travellers aged between one and 40 years
- HAV immunisation should ideally be administered not later than two weeks from departure and preferably four weeks prior to departure
- children younger than five years have a low risk for symptomatic disease if infected
  - prevention of infection in these children may protect adult contacts
- post-exposure prophylaxis
  - the HAV vaccine is not inferior to HNIG if administered within 14 days of exposure in healthy individuals aged between one and 40 years[12,13]
  - administer single antigen vaccines only - combination vaccines have reduced immunogenic content
  - immunoglobulin should be offered post exposure to children younger than two years, adults over 40 years and any immunocompromised individual

4.6.3 Response to HAV outbreaks: NOTIFY local outbreak response team according to outbreak response guidelines (epidemic preparedness and response)

4.7 Treatment of HAV:

- no specific antiviral treatment for HAV infection
- treatment is supportive with intravenous injection (IVI) fluids if persistent vomiting
- hospitalise patients with severe symptomatic disease - Jaundice and associated nausea and vomiting
- liver transplantation - should be considered in patients presenting with fulminant liver failure
- hospitalised cases do not usually require isolation unless they are faecally incontinent
- sanitary disposal of faecal waste and strict hand hygiene is essential
- no special diet is required, but it is recommended that patients should avoid alcohol and the use of any other hepatotoxic drugs
- exclusion from work and school for two weeks after the onset of jaundice, provided the AST and ALT levels are less than 100 U/L
- transaminases should normalise before adults return to fulltime work
- if adults return to work too early, they are at increased risk of developing relapsing hepatitis and this significantly delays return to fulltime work
- patients can return to active sport or strenuous activity once AST and ALT levels have normalised
- adults should return to fulltime work before returning to sport

4.8 Diagnostic, Primary, Secondary and Tertiary Levels of Care

4.8.1 Diagnosis:

- all levels of care: Anti-HAV IgM and anti-HAV IgG

4.8.2 Assessment of clinical severity:

- all levels of care: Liver profile and INR

4.8.3 Prevention:

- all levels of care
  - o screening and administration of HAV vaccine or HNIG as indicated to contacts
  - o administration of HAV vaccine to high-risk groups

4.8.4 Treatment options:

- primary level care: Uncomplicated cases
- secondary level care:
  - o symptomatic cases with jaundice, nausea and vomiting; but no encephalopathy and INR of less than two: Intravenous fluids and monitoring of synthetic function
  - o Cholestatic hepatitis: Exclude other causes of cholestasis
  - o Relapsing HAV: Exclude other causes of hepatitis, especially autoimmune hepatitis. Refer to tertiary level of care if other causes of liver dysfunction identified or there is more than one relapse or clinical deterioration
- tertiary level care:
  - o symptomatic cases not settling on supportive care
  - o acute liver failure (jaundice, encephalopathy and INR of more than 1.5): Preferably with potential access to liver transplantation
  - o recurrent relapses of HAV

HEPATITIS B (HBV)

CHAPTER 5

5.1 Introduction

HBV is an entirely vaccine-preventable disease. Patients with chronic HBV infection have a 15 to 40 per cent risk of developing cirrhosis, liver failure and/or HCC, and a 15 to 25 per cent risk of dying from HBV-related liver diseases[1].

In a recent systematic review based on observational studies performed in the general population amongst blood donors, healthcare workers and pregnant women between 1965 and 2013, South Africa had an estimated 6.7 per cent HBsAg seroprevalence i.e high intermediate endemnicity[2]. More recent studies have shown that HBsAg prevalence in adults ranges from three to 25 per cent, with the highest rates in HIV-infected adults[3-8]. HIV/HBV co-infection increases the potential risk of perinatal HBV transmission and is associated with a more aggressive natural history of chronic HBV[9]. HBV endemnicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged between five and nine years and adults[10].

5.2 HBV Genotypes

HBV is an enveloped partially double-stranded DNA virus belonging to the *Hepadnaviridae family* and is able to survive in dried blood for longer than one week. Globally, there are 10 genotypes (A-J)[11,12] and the HBV genotypes influence the spectrum of disease, the risk of hepatocellular carcinoma and the response to antiviral treatment.[12-14] Genotypes A, D and E are the predominant HBV genotypes in Africa.[12, 15]

In South Africa, Genotype A (subtypes A1 and A2) predominates with subtype A1 occurring in up to 97 per cent of rural Africans[15.16]. Varying amounts of Genotype D (less than 10 per cent) and E are reported, and odd cases of imported Genotypes B and C have been encountered, usually in patients from South-East Asia[17].

Genotype A predisposes to chronicity with an elevated risk of hepatocellular carcinoma, but has an increased response rate to interferon therapy. The relative risk of HCC is four times higher in black South Africans with Subgenotype A1 than non-A[16].

Genotype D has a reduced response rate to interferon therapy, and acute infection is associated with increased risk of acute liver failure.

5.3 Transmission of HBV

HBV IS A 100 TIMES MORE INFECTIOUS THAN HIV AND 10 TIMES MORE INFECTIOUS THAN HCV. HBV IS PREVENTABLE THROUGH IMMUNISATION.

HBV is transmissible via perinatal, percutaneous or sexual exposure to HBV-infected body fluids including serum, saliva, semen and vaginal fluids **(Table 2)**. All HBsAg-positive individuals are infectious, but HBeAg-positive individuals are more infectious as they have higher rates of HBV replication.

Table 2: Routes of transmission

Routes of transmission			
Horizontal	**Perinatal**	**Sexual**	**Percutaneous**
Occurs mainly through accidental exposure to infected blood and body fluids. Main route of HBV transmission in South Africa. Ages: Mainly less than five years old[17-20] from unapparent percutaneous exposure to infected blood or body fluids from: o infected older siblings playmates - childcare centres and schools • Sharing of personal items: o toothbrushes o razors o hair clippers • Traditional scarification practices • Female genital mutilation	Occurs at birth. High viral load (>200 000 IU/ml) increases risk of transmission7,21-25 Risk of chronic HBV infection at six months in the absence of any intervention: 70 to 95 per cent in babies born to HBeAg-positive mothers less than 10 per cent in babies born to HBeAg-negative mothers unless HIV co-infected or HBV DNA >200 000 IU/ml • Risk of transmission from women acutely infected in first or second trimester is low, but increases to approximately 60 per cent if acute infection occurs in the third trimester • Maternal HIV/HBV co-infection increases risk of perinatal transmission up to 2.5 fold [8,27-31]	Efficiently transmitted sexually. Exact risk of transmission per sexual contact is unknown A large number of non-immune adults remain at risk of sexually acquired HBV infection o No adult HBV vaccine catch-up programme	Risk of transmission from needle stick injury is:[32] 30 to 60per cent from exposure to HBeAg-positive blood • 10 to 30 per cent with HBeAg-negative blood • Injection drug use poses a high risk of HBV transmission

5.4 Clinical Presentations of HBV

The clinical manifestations of acute and chronic HBV infections are variable. **(Table 3)**

The risk of chronicity is dependent on age of acute infection:

- 70 to 95 per cent for infants exposed perinatally (HBeAg-positive mother)
- 25 to 50 per centr for children aged between one and five years
- six to 10 per cent for five to 20 years
- one to three per cent for adults older than 20 years

Acute HBV:

- clinical manifestations of acute HBV depend on the age of acquisition (incubation period ranges between one to four months)
  - anicteric, asymptomatic condition in about 70 per cent individuals, especially if infected at birth or during early childhood
  - symptomatic, icteric illness in 30 per cent and fulminant hepatitis in 0.5 to one per cent
- acute HBV infection in adolescents and adults is usually symptomatic, has various phases and is usually associated with full clinical recovery

Table 3: Acute, fulminant and chronic HBV infection

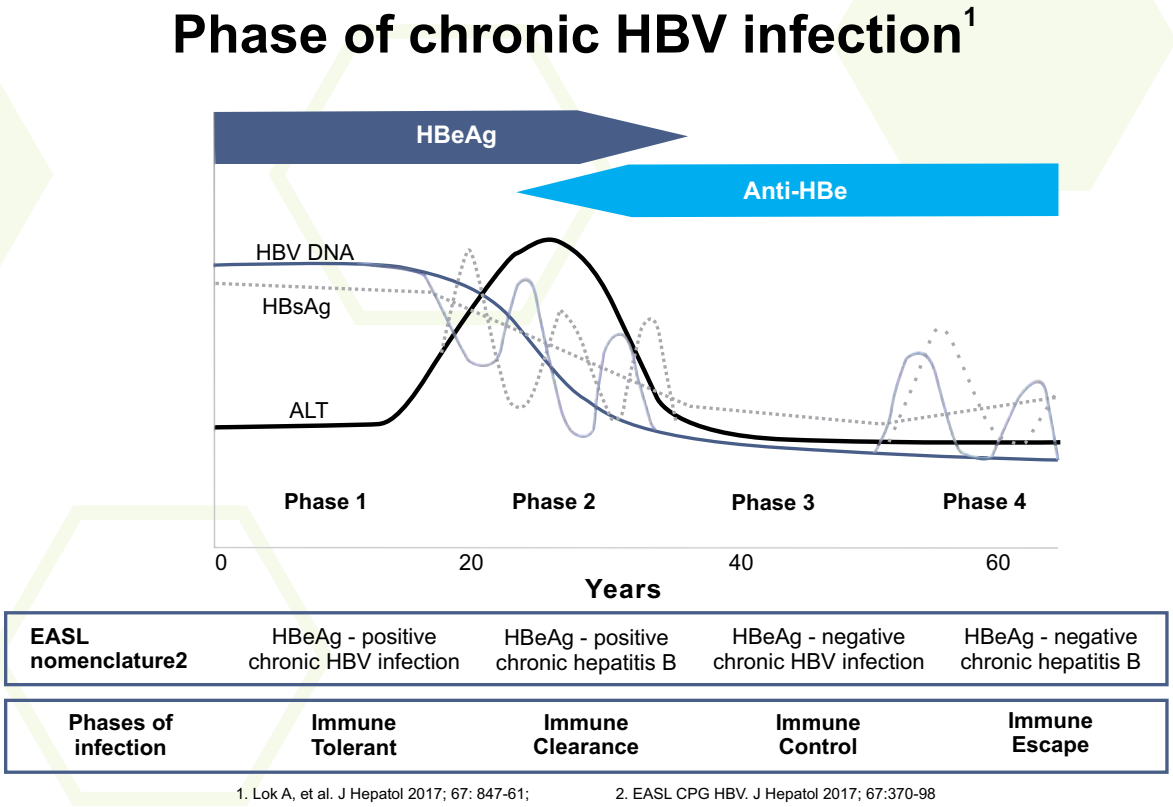
Acute HBV infection			
Early prodromal phase	**Preicteric phase**	**Icteric phase**	**Convalescent phase**
In symptomatic cases: The illness may be heralded by a serum sickness-like syndrome which precedes jaundice by 14 to 21 days and disappears with the onset of jaundice: • fever • urticaria • arthralgia and arthritis	An abrupt or insidious onset of non-specific constitutional symptoms or an influenza-like illness may occur: • malaise and fatigue • myalgia • anorexia, nausea, vomiting • epigastric or right upper quadrant discomfort Physical examination: • may be unremarkable or may reveal a tender hepatomegaly and splenomegaly • hepatosplenomegaly is usually mild (liver palpable two to three centimetres below the costal margin and spleen tipped)	• With the onset of jaundice approximately a week after the preicteric phase; fever and constitutional symptoms subside. • Anorexia, nausea and vomiting may transiently worsen. • The presence of dark urine and pale stools often raises the clinical concern of obstructive jaundice. • Pruritic scratch marks may be present, if jaundice is severe or prolonged • Weight loss is common.	• Jaundice tends to wane rapidly over days in young individuals, but tends to persist longer (six weeks or more) in adults. • The preicteric phase symptoms disappear, pruritis abates and the hepatosplenomegaly gradually resolves.

Fulminant HBV		
Syndrome is haracterised by: • jaundice • hepatic encephalopathy • Coagulopathy (INR is more than1.5) Occurring within eight weeks of the onset of the acute illness	Complications of acute liver failure include: • development of acute portal hypertension • hepatorenal syndrome • cardiorespiratory dysfunction • metabolic disturbances, including hypoglycaemia • raised intracranial pressure • life-threatening cerebral oedema • susceptibility to bacterial and fungal infections	• Survival rates: 12 to 36 per cent • Liver transplantation: Excellent outcomes if HBV DNA is undetectable and appropriate antiviral prophylaxis given

Chronic HBV		
Persistence of HBsAg-positivity for six or more months: • frequently a clinically silent disease • often identified incidentally during blood donation screening or during routine health/insurance examinations Physical examination • may reveal no or few signs • peripheral stigmata of chronic liver disease: spider naevi and palmar erythema may be present • signs of portal hypertension: Distended abdominal veins, caput medusa, ascites and splenomegaly may be present depending on the phase of chronic infection • concern for HCC: Weight loss, jaundice and rapidly enlarging, tender, hard nodular liver together with a systolic bruit	Natural history:[33,34,39, 40] • there are five different phases of chronic infection **(Figure 1)** o HBeAg-positive chronic HBV infection (immune tolerant) o HBeAg-positive chronic HBV (immune clearance) o HBeAg-negative chronic HBV infection (immune control) o HBeAg-negative chronic HBV (immune escape) o Occult HBV • natural history of HBV is dynamic and complex, and may progress non-linearly through the five different phases o not every person with chronic HBV will evolve through all the phases o some persons will be in the "gray zone" where their ALT and HBV DNA levels fall into different phases[34] o longitudinal follow up of ALT and HBV DNA levels is necessary to establish the phase of chronic infection[34] • HBV DNA levels, ALT levels and HBeAg status are important determinants of the risk of cirrhosis and need for treatment[35, 36]	Outcomes of untreated chronic HBV: • HBsAg clearance (whether spontaneous or after antiviral therapy) reduces the risk of hepatic decompensation and improves survival • approximately 0.5 per cent of persons with HBeAg-negative infection (immune control phase) will spontaneously clear HBsAg annually and develop anti-HBs • cumulative five-year incidence of cirrhosis: eight to 20 per cent • amongst those with cirrhosis: o five-year cumulative risk of hepatic decompensation: 20 per cent o risk of HCC is two to five per cent1,40,41 • HBV DNA more than 2 000 IU/ml, HBeAg status and cirrhosis are key predictors of HCC risk[35-38]. • cumulative five-year survival for compensated cirrhosis is 85 per cent, and for decompensated cirrhosis is 14 to 35 per cent[42]

Extrahepatic manifestations	
Acute infection: • serum sickness-like syndrome, more common in young adults	Chronic infection (10 to 20 per cent of patients): • polyartertis nodosa • membranous glomerulonephritis • membrano-proliferative glomerulonephritis

Figure 1: Phases of chronic HBV infection [33,34]



It is important to establish the phase of chronic infection as this determines the risk of cirrhosis and HCC, the frequency of follow up and the need for treatment.

Even if the individual clears HBsAg, the hepatocyte still harbours intranuclear covalently closed circular DNA (cccDNA) which is the transcriptional template for the viral messenger RNAs (mRNAs)[39] and this determines the chronicity and the inability to cure HBV with present day therapies. HBV DNA can also integrate into the hepatocyte genome during chronic infection. This integrated DNA plays no role in viral replication, but plays an important and ill-defined role in the development of HCC.

5.5 Hepatocellular Carcinoma

In South Africa, HCC occurs more commonly in rural-born and rural-living black men.[45] HCC accounts for one-fifth of cancers amongst men and is an aggressive tumour with coexisting cirrhosis occurring in only 60 per cent of patients with chronic HBV.

- risk factors:
  - black race
  - HBV: Genotype A, subgenotype A1 and occult HBV
  - HBV T1762 and A1764 basal core promoter mutations
  - aflatoxin B1 exposure, dietary iron overload, alcohol
  - HCV co-infection
  - HIV co-infection

- management options in advanced HCC are often extremely limited given that complex hepatobiliary surgery, transplantation, interventional radiology and sorafenib are only available in a very limited number of centres
- mean five-year survival rate varies between 25 and 60 per cent depending on tumour resectability
  - non-resectable tumours: Mean survival as low as five months
  - HCC screening: Six-monthly serum AFP and liver ultrasound examinations recommended:
  - all chronically HBV-infected individuals older than 30 years
  - all cirrhotics regardless of age
  - individuals with a family history of HCC regardless of age

In an ideal clinic setting, the combination of serial serum AFP estimation and liver ultrasound examinations has 70 per cent detection sensitivity for HCC[46]

5.6 Diagnosis of Acute and Chronic HBV [33,34,47-49]

HBV surface antigen (HBsAg) is the key marker in the diagnosis of HBV infection.

Careful interpretation of transaminases, HBV serological markers, HBV DNA levels and non-invasive markers of fibrosis or liver biopsy helps to distinguish between acute infection, resolution of acute infection, fulminant hepatitis, different phases of chronic infection and immunisation status.

5.6.1 HBV serological markers

Table 4: HBV serological markers

HB V serological markers	
HBsAg	• screening marker of infection • first serological marker to appear • may be absent during the window phase of acute infection and in fulminant hepatitis • surrogate marker for transcriptionally active cccDNA • infection is considered chronic if HBsAg persists for more than six months
HBeAg	• indicates active replication of virus • absent or low in pre-core or basal core promoter mutations
anti-HBc total (HBcAb total)	• includes both IgG and IgM HB core antibody
IgG anti-HBc	• most sensitive marker of past exposure to HBV as anti-HBs may be undetectable if HBV infection was acquired in childhood, as is common in South Africa
IgM anti-HBc	• marker of acute infection or reactivation • strongly positive in acute infection and possible low positivity in HBV reactivation or flare [50]
anti-HBs (HBsAb)	• recovery and/or immunity to HBV • detectable after immunity is conferred by HBV immunisation
anti-HBe (HBeAb)	• HBeAg to anti-HBe seroconversion and usually indicates that the virus is no longer replicating • also present in HBeAg-negative chronic HBV with active replication due to precore or basal core promotor mutants

5.6.2 Virological evaluation of HBV infection:

- serum HBV DNA quantification
- HBV genotype testing: Useful when deciding on potential efficacy of interferon therapy (tertiary care level)
- HBV resistance testing (tertiary care level)

5.6.3 Role of HBV DNA testing:

- differentiates between occult HBV (HBsAg-negative, anti-HBs-negative, IgG anti-HBc-positive, HBV DNA-positive, but less than 200 IU/ml) and resolved infection (HBsAg-negative, anti-HBs-positive, IgG anti-HBc-positive,HBV DNA undetectable)
- differentiates HBeAg-negative chronic HBV (HBV DNA 2 000 or more IU/ml) from HBeAg-negative chronic HBV infection (immune control phase - HBV DNA less than2 000 IU/ml)

- changes in HBV DNA levels used to monitor response to therapy
- in patients adherent to therapy, increasing HBV DNA levels indicate the emergence of resistant variants - in patients on TDFor TAF that have a high genetic barrier to resistance, need to strongly suspect non-adherance
- HBV DNA levels correlate with disease progression35,36

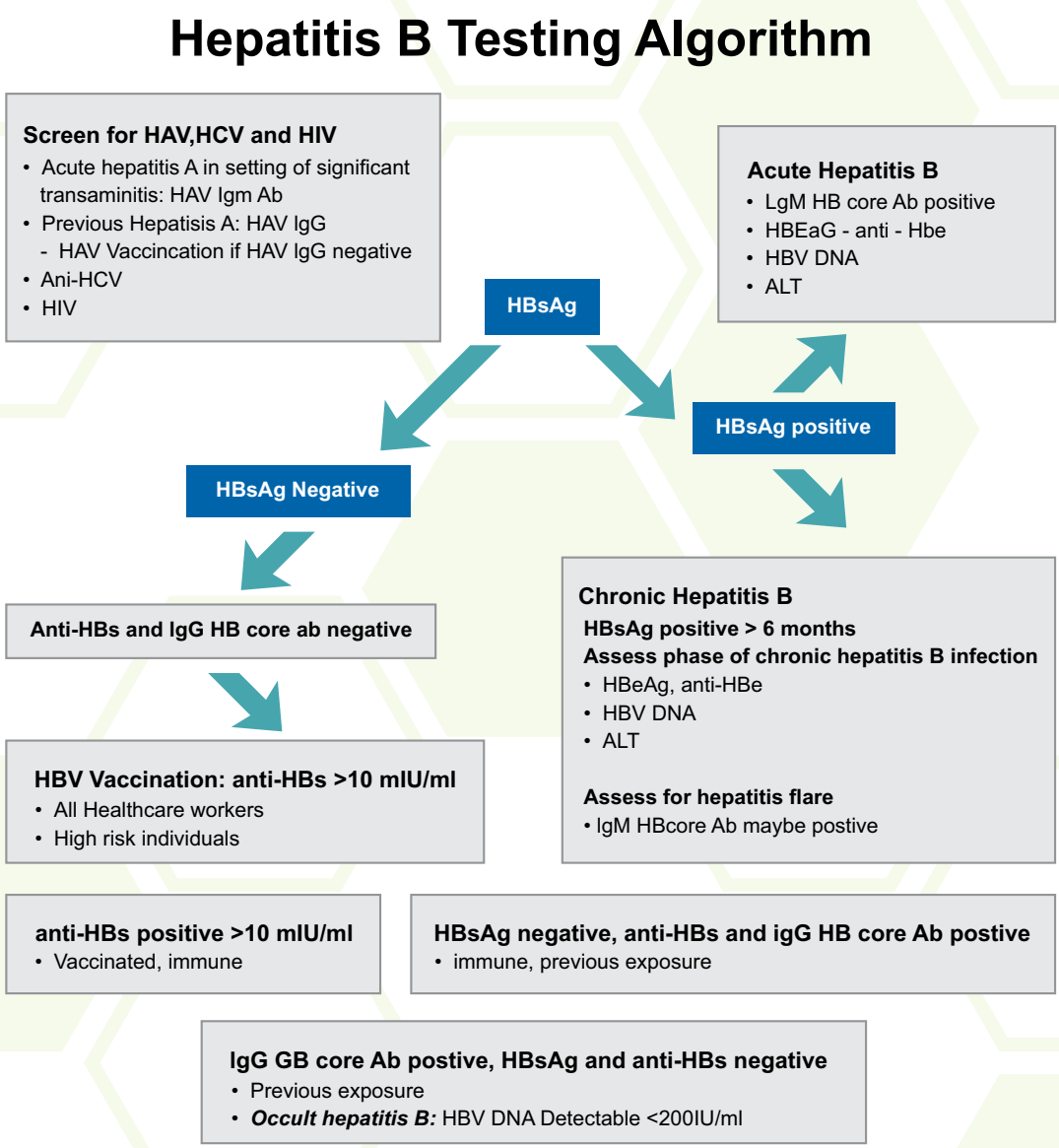
5.6.4 Interpretation of serological markers, HBV DNA and ALT levels

Table 5: Interpretation of serological markers, HBV DNA and ALT levels

Intepretation of serological markers, HBV DNA and ALT levels	
Successful immunisation	• Positive anti-HBs, protective titre more than 10 mIU/ml
Previous exposure to HBV	• Positive IgG anti-HBc +/- positive anti-HBs
Acute HBV	• HBsAg-positive, HBeAg-positive, IgM anti-HBc-positive, elevated ALT
Fulminant HBV	• May be HBsAg-negative, but IgM anti-HBc-positive, HBV DNA detectable, elevated ALT with synthetic dysfunction (elevated ammonia and prolonged INR more than 1.5)

Chronic HBV: HBV serology, ALT and HBV DNA levels depends on the phase of chronic infections	
HBeAg-positive chronic HBV infection (immune tolerant phase)	• HBsAg-positive, HBeAg-positive, anti-HBe-negative,high HBV DNA levels (usually more than 200 000 IU/ml, typically more than one million IU/ml) and normal ALT
HBeAg-positive chronic HBV (immune clearance phase)	• HBsAg-positive, HBeAg-positive, anti-HBe-negative, HBV DNA 20 000 or more IU/ml, elevated ALT
HBeAg-negative chronic HBV infection (immune control phase)	• HBsAg-positive, HBeAg-negative, anti-HBe-positive, HBV DNA less than 2 000 IU/ml, normal ALT
HBeAg-negative chronic HBV (immune escape phase)	HBsAg-positive, HBeAg-negative, anti-HBe-positive, HBV DNA 2 000 or more IU/ml, fluctuating elevated T ALT levels, IgM anti-HBc maybe low positive with a flare
Occult HBV infection	HBsAg-negative, anti-HBs-negative, IgG anti-HBc-positive, HBV DNA less than 200 IU/ ml, normal ALT

Figure 2: HBV testing algorithm



5.7 Goals and Endpoints of Therapy [33,34,47,48,51]

HBV infection cannot be eradicated completely with current available therapies because of the persistence of cccDNA, the transcriptional template of HBV, in the hepatocyte nucleus, even in individuals with serological markers of resolved infection.[56] A virological cure defined as viral eradication with elimination of cccDNA is not yet possible.

At present, the ideal endpoint of treatment is a functional immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to anti-HBs antibodies, as HBsAg is a surrogate marker for transcriptionally active cccDNA.[57,58]

5.7.1 Goals of therapy:

a) prevention of long-term complications of chronic HBV[33,35,36,59]

- cirrhosis
- liver failure
- hepatocellular carcinoma

b) prevention of HBV reactivation in the setting of immunosuppression/biologicals/chemotherapy[60]

- HBeAg-positive and HBeAg-negative chronic HBV (immune clearance and immune escape phases)
- HBeAg-positive chronic HBV infection (immune tolerant phase)

- HBeAg-negative chronic HBV infection (immune control phase)
- occult HBV

c) ensure HBV suppression in acute liver failure

- to prevent recurrence post liver transplantation

d) HIV/HBV co-infection

- dual viral suppression

5.7.2 Endpoints of treatment:

- the ideal endpoint is sustained off-therapy HBsAg loss with/without the development of anti-HBs
- durable suppression of HBV DNA to undetectable or low (below 2 000 IU/ml) levels
- normalisation of ALT
- durable HBeAg loss and seroconversion to anti-HBe in HBeAg-positive disease

5.8 Management of Acute HBV [33,34,48]

Treatment is largely supportive:

- more than 95 per cent of immunocompetent adolescents and adults will spontaneously recover, clear HBV and seroconvert to anti-HBs
- infection control measures to prevent secondary transmission especially to sexual partners must be implemented

Pegylated-Interferon therapy is contraindicated:

- exarcerbates hepatic necro-inflammation and precipitates acute liver failure, particularly in individuals with synthetic dysfunction

The use of nucleoside/tide analogues such as TDF, TAF, Entecavir and Lamivudine are not routinely advised. Rapid suppression of HBV DNA replication impairs the individual's cellular immune cytotoxic response directed against the infected hepatocytes and promotes chronic infection.

Table 6: Management of acute HBV

NUC therapy currently ONLY recommended in acute infection if:	
• Severe disease (rising INR more than two and associated encephalopathy). • Acute liver failure: - patients can stabilise and NUCs prevent re-infection of the liver graft • The elderly and immunosuppressed individuals. • HAV, HCV or HDV co-infection.	• Lamivudine should be used in unstable patients at risk of renal impairment: - rapidly suppresses HBV viral load - viral resistance does not develop with short term LAM use and dosage can easily be adjusted according to renal function
NUC therapy TDF, TAF, Entecavir and Lamivudine should be continued for:	
• three to six months after seroconversion to anti-HBs • 12 months after anti-HBe seroconversion without HBsAg loss • indefinitely, if the patient undergoes liver transplantation	

5.9 Management Of Chronic HBV

It is important to establish the phase of chronic HBV and the need for anti-viral therapy depending on disease activity, HBV DNA level, the presence of advanced fibrosis/cirrhosis or the use of immunosuppressive therapy.

Fibrosis can be assessed by non-invasive means: APRI or FIB4 score or a Fibroscan.

A liver biopsy is only required if considering Pegyllated-Interferon therapy or if assessing the role of other cofactors e.g. non-alcoholic fatty liver disease, alcohol, drugs/toxins and iron overload.[52,53] These patients should be referred to tertiary level care.

Table 7: Assessment of liver disease prior to therapy [33,34,48,49,51-54]

Assessment of liver disease prior to therapy [33,34,48,49,51-54]	
Detailed clinical history and physical examination	• age and disease duration • complications of chronic HBV • assessment of compliance with follow-up visits and medications is important • family history of HBV infection; and complications of cirrhosis and HCC
Assessment of the severity of the liver disease	• full blood count (FBC) and differential count • liver profile: Total bilirubin, conjugated bilirubin, ALT, AST, ALP, GGT - aminotransferase levels (ALT and AST) may fluctuate over time - single ALT and AST measurements do not indicate disease activity - ALT levels usually higher than AST, but with disease progression to cirrhosis, AST/ALT ratio ratio may be reversed, but less than two • serum albumin and INR to assess synthetic function • serum creatinine
Look for other co-factors that accelerate fibrosis	• viral co-infection: HCV, HDV, HIV • non-alcoholic fatty liver disease and alcohol-related liver disease • iron overload and drug/toxin-induced liver injury
Serological assessment	• HBsAg, HBeAg and anti-HBe ± IgM anti-HBc (low positive with a flare) • IgG anti-HBc (if assessing for occult HBV or previous cleared infection) • Anti-HAV IgG to assess need for HAV immunisation • HIV status
Virological assessment	• serum HBV DNA quantification • HBV genotype is useful when deciding on potential efficacy of Interferon Rx • precore and basal core promoter mutations help to predict risk of HCC • previous exposure to Lamivudine and concerns re resistance: YMDD mutations can be measured
Alpha fetoprotein	• Alpha fetoprotein in the setting of HBV-associated multifocal HCC with a rapid doubling time, remains an important screening and diagnostic tool for HCC in South Africa • may be elevated in a hepatitis flare
Ultrasound of the liver and dopplers	• assessment of liver size, contour, echogenicity and presence of focal lesions • assessment of bilary system • assessment of portal vein flow, thrombosis, splenomegaly and splenic varices
Non-invasive tests (NITs) to assess stage of liver disease [54,55] NIT results may be impacted by intercurrent diseases that may falsely increase or decrease the scores:[54,55]	• blood and serum markers for fibrosis (APRI and FIB4) can be measured, or transient elastography (Fibroscan) can be performed to rule out advanced fibrosis and cirrhosis • NITs are validated in adults with chronic hepatitis B (CHB), but not validated to assess all stages of fibrosis/cirrhosis

<table>
<tr><th colspan="2">Assessment of liver disease prior to therapy [33,34,48,49,51-54]</th></tr>
<tr><td rowspan="2">• heavy alcohol intake (AST elevation from alcoholic hepatitis)
• use of drugs and traditional herbal medicines may increase ALT and AST
• malaria or HIV (may decrease platelet count)
• hepatitis flares or acute hepatitis, congestive heart failure or a recent meal may increase liver stiffness (fibroscan)
• NITs have good diagnostic accuracy for excluding advanced fibrosis and cirrhosis

Use alongside clinical criteria and other laboratory criteria (abnormal ALT and ongoing HBV replication to identify those in need of treatment.

• APRI is WHO preferred NIT to assess fibrosis[54]
Online calculator for APRI: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
Online calculator for FIB4: https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4</td><td>a) blood/serum-based tests
APRI =(AST/ULN) x 100) / platelet count (109/L)
• validated for the diagnosis of both significant fibrosis ≥F2 and cirrhosis (F4)
• Single high cut-off >2 for identifying adults with cirrhosis (F4) and in need of antiviral therapy
• adults with an APRI score of >2
o detects only one third of persons with cirrhosis</td></tr>
<tr><td>b) transient elastography measures liver stiffness[55]
• Fibroscan (range is between 0 and 75 kPa)
• Single cut-off value: Significant fibrosis (≥ F2) >7- 8.5 kPa and Cirrhosis (F4) >11-14 kPa
• Mean cut-off of 12.5 kPa to diagnose cirrhosis Sensitivity is improved when combined with non-invasive biomarker scores</td></tr>
<tr><td>Liver biopsy</td><td>• a liver biopsy is only required if considering Pegylated Interferon therapy or if assessing the role of other co-factors e.g. non-alcoholic fatty liver disease, alcohol, drugs/toxins and iron overload. These patients should be referred to tertiary level care</td></tr>
<tr><td>Endoscopy</td><td>• to assess for varices in cirrhotic individuals</td></tr>
</table>

5.10 Treatment Options for Chronic HBV

The recommended first-line monotherapies include Pegylated-Interferon and the NUCs, TDF, TAF and Entecavir that have a high genetic barrier to resistance.

All patients with chronic HBV are potential treatment candidates, but it is essential to choose the appropriate treatment at the appropriate time.

It is important to assess the clinical situation and not only the HBV viral load.

A liver biopsy is mandatory when considering treatment with Pegylated-Interferon alpha-2a.

5.10.1 Pegylated-Interferon[33,34,79-83]

- Favourable predictors for response to Pegylated-Interferon: Young individuals, ALT >2 - 5 x ULN, active necro-inflammation on liver biopsy (Metavir Grade ≥A2) and Genotype A and B > C and D
- PegIFN alfa-2a 180 µg/wk by subcutaneous injection for 48 weeks
- Yields HBeAg seroconversion in 20 to 31 per cent and sustained off-treatment HBV DNA suppression less than 2 000 IU/mL in 65 per cent who achieve HBeAg to anti-HBe seroconversion
- Monitoring during treatment:
  - full blood count every one to three months
  - liver profile and TSH every three months
  - HBsAg concentration and HBV DNA levels at 12, 24 and 48 weeks to determine virological response

- clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
- Potential AEs: Influenza-like symptoms, fatigue, mood disturbances, cytopenia, and autoimmune disorders in adults

Most patients in South Africa do not meet the clinical criteria for Pegylated-Interferon.

- These patients should be referred to tertiary level care for assessment and management [33,34]

5.10.2 Nucleos(t)ide analogue therapy[33,34,54]

The majority of patients are candidates for nucleos(t) ide analogue therapy

- Long-term (potentially indefinite) treatment.
- Aim for on-treatment viral suppression (HBV DNA undetectable).
- Maintained through continuous antiviral therapy.
- Suppression of replication to undetectable levels to avoid resistance.

Table 8: Nucleos(t)ide analogue options for chronic HBV and dosage regimens[33,34,48,49]

Nucleos(t)ide analogue options for chronic HBV and dosage regimens33,34,48,49,54	
TDF	• recommended dosage for adults with normal renal function (creatinine clearance >50 ml/min): 300 mg per day • dosage reduction necessary in patients with impaired renal function
TAF	• adults or adolescents (aged ≥12 years and ≥35 kg body weight) • dosage : 25mg daily • recommended in individuals >60 years • recommended for adults with impaired renal function - eGFR <60ml/min/1.73m2 - albuminuria >30 mg/24 hrs or moderate dipstix proteinuria - hhaemodialysis - low phosphate • recommended in adults with bone disease - chronic steroid use - osteoporosis - history of fragilty fracture • requires Section 21 application to SAHPRA
Entecavir	• recommended dosage for adults with normal renal function: eGFR >50 ml/min - 0.5mg daily if Lamivudine naïve 1mg daily if previously exposed to Lamivudine or if Lamivudine refractory or resistant * • dosage reduction necessary in patients with impaired renal function **
Lamivudine	• recommended dosage for adults with normal renal function: 100 mg/day (creatinine clearance >50 ml/min) • HIV/HBV co-infection: 300mg Lamivudine daily61 • recommended dosage for children: 3 mg/kg/day, maximum dosage 100 mg/day • dosage reduction necessary in patients with impaired renal function • recommended in unstable patients with renal impairment – resistance 20per cent at six months61, if Entecavir or TAF not available

* TAF is preferred to ETV in patients with previous exposure to NAs
* * ETV dose needs to be adjusted if eGFR <50 ml/min
No dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis
EASL CPG HBV. J Hepatol 2017;67:370–98.

5.11 Definitions of Treatment Response for Nucleostide Analogue (Nuc)Therapy [33,34,49]

Responses may be biochemical, serological, virological or histological and vary according to the type of therapy.

Table 9: Definitions of treatment response to NUC therapy

Term	Definition
Biochemical response	• normalisation of ALT levels (<25 U/L in females and <35 U/L in males) • a minimum follow-up of at least one year post treatment with ALT determinations every three months is required to confirm sustained off-treatment biochemical response
Serological response for HBeAg	• HBeAg loss and HBeAg seroconversion to anti-HBe positive
Serological response for HBsAg	• HBeAg loss and HBeAg seroconversion to anti-HBe positive • HBsAg loss and development of anti-HBs • undetectable HBV DNA by a sensitive PCR assay with limit of detection of 10 IU/ml • applies to all patients with chronic HBV
Virological response during NUC therapy	• undetectable HBV DNA by a sensitive PCR assay with limit of detection of 10 IU/ml
Sustained off-therapy virological response	• serum HBV DNA <2000 U/ml for at least 12 months after end of therapy
Complete response	• sustained off-treatment virological response together with loss of HBsAg
Primary non-response	• <1 log10 IU/ml decrease in HBV DNA levels from baseline at three months of therapy
Partial virological response	• detectable HBV DNA, but >1 log10 IU/ml decrease in HBV DNA levels • should be assessed at 24 weeks for patients on lamivudine, which is moderately potent, but has a low genetic barrier to resistance and at 48 weeks in patients on Entecavir, TDF and TAF which are highly potent with a higher genetic barrier to resistance
Persistent viraemia	• in patients on entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide is defined as a failure to achieve undetectable HBV DNA after 96 weeks of treatment • Should raise concerns of non-adherance
Virological breakthrough	• confirmed increase in HBV DNA level >1 log10 IU/ml compared with the nadir HBV DNA level on therapy or HBV DNA >100 IU/ml in individuals on therapy with previously undetectable levels (<10 IU/ml). • usually precedes a biochemical breakthrough • main causes of virological breakthrough are poor adherence to therapy or the development of resistance
Resistance	• may result in primary treatment failure or virological breakthrough on therapy
Histological response	• decrease in necro-inflammatory activity by ≥2 points in histological activity index without worsening of fibrosiscompared to pre-treatment histological findings

5.12 Indications for Treatment

33,34,54,74

5.12.1 Patients who must be treated:

33,34,48,49,51,54,57-60,70-74

- acute liver failure: In order to suppress ongoing HBV replication in an attempt to prevent ongoing hepatocyte necrosis or to render HBV DNA undetectable prior liver transplantation
- clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on an APRI score of more than two in adults) regardless of ALT levels, HBeAg status or HBV DNA levels
- HBeAg-positive chronic HBV (immune clearance phase)
- HBeAg-negative chronic HBV (immune escape phase)
- all HBV-infected individuals receiving chemotherapy, rituximab or immunosuppressive therapy regardless of the phase of infection
- select group of immune-tolerant adults (HBeAg-positive chronic HBV infection) older than 30 years of age:
  - normal ALT and elevated HBV DNA (1 000 000 IU/mL)
  - Fibroscan showing significant fibrosis or liver biopsy specimen showing significant necroinflammation or fibrosis
- additional factors to be considered when deciding on treatment:
  - age, family history of HCC or cirrhosis, previous treatment history, presence of extrahepatic manifestations
- ff treatment not indicated, actively monitor as candIcacy for treatment may change with disease progression

Table 10: Recommendations for treatment: Non-cirrhotic HBeAg-positive patients [33,34,49,54]

HBV DNA[a]	ALT[b]	Treatment strategy
≥20 000 IU/ml	Normal	HBeAg-positive chronic HBV infection (immune tolerance): • younger patients often immune tolerant (HBV DNA usually >200 000 IU/ml and typically >1x 106 IU/ml) • low rate of HBeAg seroconversion for all therapies • monitor ALT and HBV DNA every three to six months for one year, then six-monthlyb • monitor HBeAg annually No treatment required if persistently normal ALT • consider treatment if >30 years and evidence of fibrosis on Fibroscan or histologically or family history of HCC or cirrhosis
≥20 000 IU/ml	ALT >ULN but <2x ULN	• exclude other causes of ALT elevation - treat if ALT elevation persists, especially if >30 years of age • evaluate fibrosis/inflammation - Treat if ≥F2 or ≥A3 • TDF, Entecavir, Peginterferon-2a: Preferred first line therapycd • NUC therapy: Continue for 12 months after HBeAg seroconversion to anti-HBe and HBV DNA undetectable
≥20 000 IU/ml	≥2x ULN	HBeAg-positive chronic HBV (immune clearance): Needs treatment • liver biopsy only required for Pegylated-Interferon-based therapy or if other causes of liver injury suspected • TDF, Entecavir, Peginterferon-2a: Preferred first line therapycd • NUC therapy: Continue for 12 months after HBeAg seroconversion to anti-HBe and HBV HBV DNA undetectable

HBV DNA[a]	ALT[b]	Treatment strategy
2000 - 20 000 IU/mL	≥2x ULN	• exclude other causes of ALT elevation - treat if ALT elevation persists, especially if >30 yrs of age • evaluate fibrosis/inflammation - treat if ≥F2 or ≥A3 • TDF, Entecavir, Peginterferon-2a: Preferred first line therapycd • this may represent HBeAg seroconversion - monitor HBV DNA every one to three months - treat if HBV DNA > 2 000 IU/mL persists for more than six months

a Values shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL).
b On initial diagnosis, ideally every three months for one year to ensure stability.
ALT ULN: 25 IU/ml (females) and 35 IU/ml (males)
c Genotyping may be useful to help decide between treating with peginterferon alfa-2a or NUC
(Peginterferon is more effective in patients with genotype A vs D)
d Peginterferon alfa-2a, entecavir, and tenofovir are preferred over lamivudine because they have been shown to be superior in randomised clinical trials and/or have lower rates of resistance

Table 11: Recommendations for treatment: Non-cirrhotic HBeAg-negative patients [33,34,49,54]

HBV DNA[a]	ALT[b]	Treatment strategy
<2 000 IU/ml	Normal	HBeAg-negative chronic HBV infection: • No treatment: Majority in immune control phase • monitor ALT and HBV DNA every three months for one year to confirm immune control phase, then six to 12-monthlyb • monitor HBsAg annually • if unable to monitor closely: Treat • consider therapy in patients with known significant histologic disease or advanced fibrosis on Fibroscan even if low-level replication and normal ALT
<2 000 IU/ml	ALT >ULN but <2x ULN	• exclude other causes of ALT elevation o treat if ALT elevation persists, especially if >30 yrs of age • evaluate fibrosis/inflammation o treat if ≥ F2 or ≥ A3
≥2 000 IU/ml	Normal	• monitor ALT and HBV DNA every three months for one year then every six months • monitor HBsAg annually • persistently elevated ALT: Treat • consider monitoring for pre-core and basal core promotor mutations which are associated with increased HCC risk: o consider treatment if high risk mutations present and fibrosis present on Fibroscan o consider treatment if family history of HCC or cirrhosis • Tenofovir, Entecavir, or Peginterferon-2a:Preferred first line therapyc • NUC therapy : Long-term treatment recommended
≥2 000 IU/ml	ALT >ULN but <2x ULN	exclude other causes of ALT elevation treat if ALT elevation persists, especially if >30 yrs of age evaluate fibrosis/inflammation Treat if ≥F2 or ≥A3

HBV DNA[a]	ALT[b]	Treatment strategy
≥2 000 IU/ml	≥2x ULN	HBeAg-negative chronic HBV (immune escape) • needs treatment • Liver biopsy only required for Pegylated-Interferon-based therapy or if other cause of liver injury suspected • Tenofovir, Entecavir, or Peginterferon-2a: preferred first line therapyc NUC therapy: Long-term treatment recommended

a Values shown in IU/mL (1 IU/mL is equivalent to approximately 5.6 copies/mL)
b On initial diagnosis, ideally every three months for one year to ensure stability
ALT ULN: 35 IU/ml in males and 25 IU/ml in females
c Peginterferon alfa-2a, Entecavir, and Tenofovir are preferred over lamivudine because they have been shown to be superior in randomised clinical trials and have lower rates of resistance.

5.12.2 Patients who do not require immediate therapy, but should be monitored [33,34,49,54]

- HBeAg-positive chronic HBV infection (immune tolerant phase): younger than 30 years old with persistently normal ALT, no evidence of liver disease, and no family history of cirrhosis or HCC
- HBeAg-negative chronic HBV infection (immune control phase): Normal ALT and HBV DNA less than 2 000 IU/ml
- Occult HBV: Only treat if on immunosuppressive therapy

5.13 Management of individuals with HBeAg-Negative chronic HBV Infection (Immune Control) or HBeAg-Positive Chronic HBV Infection (Immune Tolerant Phase) who require Immunosuppressive Therapy, Rituximab or Chemotherapy

HBsAg and IgG anti-HBc should be tested before the introduction of immunosuppressive therapy, rituximab or chemotherapy. [33,34, 75-77]

- HBsAg or IgG anti-HBc positive: HBV DNA levels should be measured
- HBsAg-negative, IgG anti-HBc positive and HBV DNA detectable: NUC therapy is indicated as for HBsAg-positive individuals
- HBsAg-negative, IgG anti-HBc positive and HBV DNA undetectable: No treatment is needed except if receiving Rituximab
- ALT and HBV DNA levels should be monitored at regular intervals (one to three-monthly) depending on immunotherapy type
- treatment should be initiated when HBV DNA becomes detectable
- if regular HBV DNA level monitoring is not possible, NUC therapy is also indicated
- HBsAg-positive and HBV DNA less than 2 000 IU/ml: Continue NUC therapy for 12 months after completion of immunosuppressive therapy
- Lamivudine can be used, if anticipated duration of treatment is not more than 12 months and HBV DNA level is less than 2 000 IU/ml
- HBsAg-positive and HBV DNA 2 000 or more IU/ml: NUC with a high genetic barrier to resistance (tenofovir or entecavir) should be used and continued until the usual treatment endpoint has been achieved
- IgG anti-HBc-positive patients receiving bone marrow or stem cell transplants should also receive NUC prophylaxis regardless of HBsAg and HBV DNA status where possible, antiviral therapy should be initiated before the onset of immunosuppressive therapy, Rituximab or chemotherapy, and HBV DNA levels should be undetectable
- if patients are unstable with impaired renal function, then treatment with Lamivudine can be initiated and TDF added once clinically stable or motivate for TAF or Entecavir

5.14 Indications for Combination Nuc Therapy

There are as yet no data confirming the advantage of combination NUC therapy as standard of care. The most commonly used combination therapies are TDF plus Lamivudine or TDF plus Emtricitabine, which may be considered in the following situations: [33,34,51,78]

- unstable patients: Lamivudine initiated for HBV viral suppression with the addition of TDF when clinically stable with normal renal function or motivate for TAF or Entecavir
- post-liver transplantation together with HBV immune globulin (HBIG)
- HIV/HBV co-infection where there is a risk of resistance with monotherapy
- suboptimal response to an initial drug, especially in the presence of high HBV DNA levels
- established resistance to an NUC

5.15 Duration of Nuc Therapy [33,34,54]

5.15.1 Life-long treatment with NUCs

- stopping antiviral therapy is associated with risk of reactivation, which can cause severe acute-on-chronic liver failure
  - cirrhosis based on clinical evidence and APRI score of more than two in adults, or on histology
  - previous hepatic decompensation

5.12.2 HBeAg-positive chronic HBV (immune clearance)

- HBeAg to anti-HBe seroconversion with persistently normal ALT and undetectable HBV DNA levels:
  - treatment with TDF or TAF or Entecavir should be consolidated and continued for at least 12 months after anti-HBe seroconversion
  - careful follow-up after the cessation of successful treatment is essential: 20 per cent of patients may relapse and become HBeAg-positive
  - after stopping NUCs, monitor every three months for at least one year for recurrent viraemia, ALT flares, HBeAg seroreversion and clinical decompensation

    continuation of therapy until HBsAg seroconversion is advisable[84] with ongoing monitoring after therapy cessation to detect HBsAg seroreversion

5.15.3 HBeAg-negative chronic hepatitis:

- life-long NUC therapy is recommended in individuals who remain HBsAg-positive
- can stop NUCs 12 months after HBsAg seroconversion with ongoing monitoring for relapse

Most patients with chronic HBV in South Africa will need life-long NUC therapy.

Where HBV DNA testing is not available discontinuation of NUC therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least 12 months additional treatment, regardless of prior HBeAg status. [54]

Discontinuation of antiviral therapy can only be considered in individuals who can be followed up regularly long term for reactivation.[54]

5.16 Monitoring On Nuc Therapy [33,34,48,49]

- FBC, differential count, INR, liver profile, serum creatinine: Baseline, week four and then three to six-monthly if stable
- TDF: Serum creatinine and phosphate and urinary protein dipstick should be measured at baseline. Subsequent frequency depends on baseline renal function and risk for renal dysfunction, but should be performed at least annually
- HBV DNA levels: Baseline and week 12 to assess virological response and then every six to 12 months
  - HBV DNA monitoring is critical to detect treatment failure
  - undetectable HBV DNA levels by real-time PCR (detection level less than 10 - 15 IU/ml) needs to be achieved to prevent the development of resistance
- partial responses (HBV DNA level detectable, but less than 2 000 IU/ ml) assessed at:
  - 24 weeks for Lamivudine

- 48 weeks for TDF, TAF and Entecavir. If HBV DNA levels are still positive, but declining at 48 weeks on TDF, TAF or Entecavir, monotherapy can be continued

- bone mineral density: Annually if risk factors for osteoporosis present
- risk factors for renal dysfunction: Decompensated cirrhosis, creatinine clearance less than 60 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation
  - NUCs require dosage adjustments in the setting of renal impairment. Consider use of TAF or Entaecavir
- if TDF associated renal dysfunction or osteoporosis occurs, TDF should be discontinued and TAF or Entecavir considered for ongoing treatment
- HCC screening: Baseline AFP and ultrasound liver every six to 12 months depending on risk factors

5.16.1 HBeAg-positive disease:

- HBeAg and anti-HBe measured every 12 months
- HBsAg should be checked six-monthly after anti-HBe seroconversion

5.16.2 HBeAg-negative disease:

- a virological response (HBV DNA less than 2 000 IU/ml) is associated with disease remission
- monitor HBsAg six-monthly, if HBV DNA levels are undetectable
- lifelong NUC therapy is recommended in individuals who remain HBsAg positive

5.17 Monitoring of Patients Not Considered for Therapy

33,34,48

5.17.1 HBeAg-positive chronic HBV infection: Immune tolerant phase (HBsAg-positive, HBeAg-positive, HBV DNA >20 000 IU/ml, normal ALT)

- ALT and HBV DNA levels: Every three to six months for one year, more often if ALT becomes elevated
  - persistently normal ALT for one year: ALT and HBV DNA every six months
  - ALT 1 - 2 x ULN, recheck ALT every one to three months
- HBeAg status: Every 12 months
- annual non-invasive monitoring of fibrosis: APRI score or Fibroscan
- evaluate for fibrosis and inflammation and consider treatment:
  - if the patient is older than 30 years of age
  - if ALT is borderline or less than 2x ULN elevated on serial tests
  - exclude other causes of ALT elevation and treat if ≥A3 or ≥F2 on histology or ≥F2 on Fibroscan
- HCC screening: Baseline AFP and ultrasound liver every six to 12 months depending on risk factors

5.17.2 HBeAg-negative chronic HBV infection: Immune control phase (HBsAg-positive, HBeAg-negative, HBV DNA <2 000 IU/ml, normal ALT)

- ALT and HBV DNA levels: Every three months for one year, more often if ALT becomes elevated
  - persistently normal ALT and HBV DNA less than 2 000 IU/ml for one year: ALT and HBV DNA every six to 12 months
  - ALT 1 - 2 x ULN: check serum HBV DNA level and exclude other causes of liver disease
- Evaluate for fibrosis and inflammation and consider treatment:
  - if ALT is borderline or mildly elevated on serial tests
  - if HBV DNA is persistently on 2 000 or more IU/ml
  - exclude other causes of ALT elevation and treat if ALT elevation persists especially if older then 30 years of age
  - treat ≥A3 or ≥F2 on histology or ≥F2 on Fibroscan
- HCC screening: Baseline AFP and ultrasound liver and every six to 12 months depending on risk factors

5.18 Management of Nucleos(T)Ide Resistance [33,34,48,54]

Drug resistance is defined as a more than one log10 IU/mL increase in HBV DNA from nadir documented on two consecutive serum samples collected at least one month apart in patients who initially responded to therapy and who have been adherent. [85].

The emergence of antiviral resistance usually leads to an increase in HBV DNA levels or viral rebound after an initial response during therapy, which is likely to be followed by biochemical breakthrough with a rise in ALT levels and, in some cases, hepatitis flares and progression to hepatic decompensation.

Elevation in ALT level tends to occur late and is a relatively poor predictive marker of resistance.

Therapy should be altered by substitution with another drug or adding to the existing regimen (preferable to add another agent to prevent rebound of wild-type virus) if:

5.18.1 Primary antiviral therapy failure:

- failure of drug to reduce HBV DNA levels by more than one x log10 IU/mL within three months following initiation of therapy
- rare in persons initiating and adherent to TDF, TAF or Entecavir therapy
- can occur in persons treated with Lamivudine, Adefovir or Telbivudine

5.18.2 Secondary antiviral treatment failure:

- rebound of HBV DNA levels of more than one x log10 IU/mL from the nadir in persons with an initial antiviral treatment effect (more than one x log10 IU/mL decrease in serum HBV DNA)

In patients on TDF, TAF or Entecavir with high genetic barrier to resistance, HBV DNA levels should be undetectable by 48 weeks. Patients with persistent low level viraemia or virological breakthrough on on TDF, TAF or Entecavir should be counseled about adherence.

In settings without access to HBV DNA testing and where treatment failure and drug resistance is suspected:

- use of antiviral drugs with a low barrier to resistance
- rising transaminases
- evidence of progressive liver disease

Table 12: Management of NUC resistance

NUC resistance	Management
Lamivudine	• add Tenofovir or switch to Tenofovir/Emtricitabine • screen for tyrosine-methionine-aspartate-aspartate (YMDD) mutations, if available
Entecavir	• add or switch to TDF or switch to TDF plus Emtricitabine • safety of an Entecavir/ Tenofovir combination is not known
TDF	• resistance has not been described up to 10 years of treatment

5.19 Treatment of Special Populations

5.19.1 Healthcare workers (HCWs):[33]

- HBsAg-positive HCWs performing exposure-prone procedures with HBV DNA levels more than 200 IU/ml: TDF or TAF or Entecavir therapy to reduce transmission risk if not requiring treatment for HBeAg-positive and HBeAg-negative chronic HBV
- HBV DNA level should preferably be undetectable or at least less than 200 IU/ml before returning to exposure-prone procedures
- HBV infection alone does not disqualify HCWs from surgery, dentistry, medicine or allied health fields

5.19.2 Pregnancy

There is no worsening of liver disease in most women, but case reports have suggested that HBV reactivation, hepatic exacerbations and fulminant liver failure may occur. There are reports of higher rates of preterm births, lower APGAR scores, gestational diabetes and antepartum haemorrhage.

HBsAg-positive mothers need close follow up during pregnancy.

HBsAg screening of pregnant women is essential: [33,34,54]

- during the first trimester of each pregnancy
- pregnant women not immune to HBV and with risk factors for infection should be vaccinated against HBV – the vaccine is safe in pregnancy
- ongoing high-risk behavior during pregnancy and HBsAg status unknown:
  - test for HBsAg at admission for delivery
- HBsAg-positive women must be referred for additional testing, counseling and medical management

Most women of childbearing age (20s and 30s) are likely to be in the immune tolerant or immune control phase and are not candidates for HBV treatment, but the risk of MTCT needs to be considered in pregnant women with high HBV viral loads (HBV DNA more than 200 000 IU/ml) in both HBeAg-negative and positive pregnant women.[33, 34]

a) acute HBV:

- antivirals are generally not recommended, unless there is evidence of acute liver failure
- patient should be monitored closely and treated conservatively
- increased risk of MTCT if the mother acquires acute HBV in the second or third trimester and if HBV DNA levels are more than 200 000 IU/ml in the third trimester - administer antivirals to prevent MTCT

b) chronic HBV:

Indications for therapy in a HBV-infected pregnant mother are the same as in other HBV-infected individuals:

- HBeAg-positive chronic HBV
- HBeAg-negative chronic HBV
- cirrhosis

c) Therapy:

- the use of Lamivudine, Emtricitabine and TDF in HIV-positive pregnant women is safe86
- drug of choice is TDF33.34,54 and has similar rates of birth defects to the general population
- no data available on safety of TAF in pregnancy
- Pegylated-Interferon is contraindicated

There is a risk of HBV flare and close monitoring is required if the mother is untreated or if antivirals are stopped during pregnancy or soon after delivery.

i. women requiring HBV treatment and considering pregnancy:

- TDF is the treatment of choice of HBV viral suppression prior to pregnancy
- increased risk of HBV MTCT in the third trimester if HBV DNA is more than 200 000 IU/ml
- can consider a finite course of pegylated IFN (if favourable clinical profile) before pregnancy

ii. pregnant whilst on HBV treatment

- TDF is the preferred NUC to maintain HBV suppression
- review type of treatment: Stop pegylated IFN and switch to antivirals, Entecavir should be switched to TDF

iii. pregnant and treatment not clinically indicated for HBV infection:

- assess risk of HBV MTCT and treat as necessary in third trimester
- refer for ongoing follow-up and assessment after delivery. HBV/HIV co-infection align with prevention of mother-to-child transmission (PMTCT) guidelines for HIV-positive pregnant women

iv. prevention of HBV MTCT - see also 5.23.4 PEP for babies born to HBV-infected women

- HBV DNA more than 200 000 IU/ml: Recommend antiviral therapy to prevent perinatal transmission87-89 regardless of HBeAg status
- TDF is the preferred agent and should be started at 28-32 weeks gestation34 - as fits best with the planned antenatal visits
- NUC therapy can be stopped 12 weeks post delivery, if only used for HBV MTCT prevention in HIV-negative pregnant women
- all neonates must receive HBV birth dose vaccine within 24 hours of delivery. Although HBIG is advised if pregnant women is HBeAg-positive, this is expensive and not readily available
- caesarean section is not indicated to prevent HBV MTCT

- breastfeeding is not contraindicated if mother is HBV virally suppressed iether on or off tenofovir disoproxil fumarate
  - if not HBV virally suppressed, bleeding, cracked nipples are a potential source of infection to neonate

5.19.3 Dialysis and renal transplant patients:[33,34]

- all dialysis and renal transplant recipients should be screened for HBsAg, anti-HBs and IgG HBV core Ab
- TAF and Entecavir should be used for prophylaxis or treatment
  - Entecavir dosages need to be adjusted in patients with impaired renal function
- HBsAg-positive dialysis patients requiring therapy should receive TAF or Entecavir
- all HBsAg-positive patients undergoing renal transplantation should receive NUC therapy as prophylaxis or treatment
- Pegylated-Interferon therapy is not recommended in renal transplant recipients because of the risk of graft rejection
- HBsAg-negative, IgG HBV core Ab positive: Treat if HBV DNA-positive and on immunosuppression

5.19.4 Children:[33,34,90]

- chronic HBV is typically benign as children are usually in the immune tolerant phase
- liver biopsy is helpful in guiding need for therapy in children with abnormal liver profiles
- treatment is recommended in HBeAg-positive children with persistently elevated ALT of more than 30 IU/ml
- HBV DNA usually more than 106 IU/ml, therefore no recommended HBV DNA threshold for treatment
- if HBV DNA is less than 104 IU/ml, defer therapy until other causes of liver disease or spontaneous HBeAg seroconversion are excluded

Treatment recommendations: [33,34]:

- Lamivudine: Children of two years and older, but long-term use of Lamivudine is associated with the development of resistance (70 per cent at five years)
- Entecavir: In children of two years and older and weighing at least 10kg. Dose is determined by weight (see package insert). Children that weigh more than 30kg receive 0.5mg daily
- TDF: 300 mg daily in adolescents of 12 years and older and 35kg or more body weight
- TAF: 25mg daily in adolescents aged 12 and older and with a 35kg or more body weight
- treatment with NUCs continued until HBeAg seroconversion followed by an additional 12 months consolidation therapy [34]
- on stopping NUC therapy, need to monitor every three months for at least one year for HBV flares and clinical decompensation
- Pegylated-Interferon-alpha-2a: 180ug/1.73m2 body surface area, maximum 180ug weekly[33]

5.19.5 HBV/HCV co-infection:

- all HBV-infected individuals must be screened for HCV
- HCV super-infection can lead to more severe acute symptoms and liver failure
- HCV super-infection also associated with HBsAg clearance, HBeAg seroconversion, and/or a reduction in HBsAg titres [91-93]
- increased risk of cirrhosis, hepatocellular carcinoma and death [94,95]
- hhistological progression over a time period as short as three years [96]
- HBV super-infection of chronically infected HCV patients can also lead to fulminant liver failure [94,97-99]

In HBV/HCV co-infection, HCV is often the dominant driver of chronic inflammatory activity[100, 101]. HBV DNA levels are usually low but HBV reactivation can occur during or after HCV clearance on DAA therapy. A meta-analysis and systematic review demonstrated that the pooled proportion of patients with HBV reactivation on DAA therapy was higher in HBsAg-positive patients: 24 per cent (95 per cent CI 19–30) versus 1·4 per cent (0·8–2·4) in those with resolved HBV infection.[138] Hence, HBsAg, anti-HBc and anti-HBs testing is recommended prior to DAA therapy. If HBsAg is positive, concurrent HBV NUC therapy is advised and HCV DAA therapy commenced once HBV DNA levels suppressed. Treatment should be continued for 12 weeks post DAA therapy with requisite monitoring after stopping, unless HBV requires longterm therapy. Serum ALT levels should be carefully monitored (baseline, end of DAA therapy and during followup) in HBsAg-negative but IgG anti-HBc-positive patients.[50]

5.19.6 HBV/HIV co-infection

Liver disease, particularly in the post antiretroviral era of HIV/AIDS, has emerged as a major cause of morbidity and mortality in HBV or HCV co-infected patients102. In contrast to developed countries, HBV/HIV co-infection outnumbers HCV/HIV co-infection in South Africa and probably reflects the present lower prevalence of injecting drug use, although this is increasing particularly in cities. There is usually independent transmission and acquisition of HBV and HIV. HBV is generally acquired in childhood under the age of five years and HIV infection occurs later in life, primarily via heterosexual sex.

HIV co-infection promotes:

- increased HBV replication and rates of HBV reactivation
- acute liver failure
- increased rates of occult HBV
- chronicity of newly acquired HBV infections
- accelerated progression to fibrosis and cirrhosis
- HCC occurs at a younger age and is more aggressive
- increased risk of ART hepatotoxicity
- ART- related immune reconstitution hepatitis

Liver-related mortality is twice as high for HBV/HIV co-infected as for HCV/HIV co-infected individuals. A CD4 count of less than 200 cells/ml is associated with a 16.2 fold increase in risk of liver-related deaths compared to a CD4 count of more than 350 cells/ml[102]. Additionally, a potential association with adverse HIV outcomes in HBV co-infected individuals was demonstrated in the SMART study where HIV-associated immune deficiency was enhanced by active HBV replication resulting in increased progression to AIDS-related outcomes and all-cause mortality.[103]

Aetiology of abnormal liver profile in HIV/HBV co-infected individuals is often multifactorial:

- drug/toxin induced liver injuries: Highly active antiretroviral therapy (HAART), tuberculosis (TB) drugs, Cotrimoxazole, Fluconazole, traditional, herbal/alternative supplements
- HIV-related opportunistic infections
- HBV clearance
- emergence of drug resistance
- immune reconstitution inflamatory syndrome (IRIS)
- reactivation after withdrawal of therapy
- super-infection with HCV, HAV, HDV and HEV
- co-morbidities: Non-alcoholic fatty liver disease, alcoholic liver disease, iron overload

As the aetiology of deranged liver enzymes is often multifactorial and in the setting of a more aggressive natural history of HBV, there should be a lower threshold for performing a liver biopsy to assess the differential diagnosis and the stage and grade of histological injury.

a) recommendations for the initiation of ART in HBV/HIV co-infection:

- South Africa follows the WHO 2016 HIV treatment guidelines to treat all people with HIV, including children and pregnant or breastfeeding women regardless of CD4 cell count

b) goals of therapy:

- virological suppression of both HBV and HIV replication
- amelioration of transaminitis and histological injury and prevention of liver-related complications

c) choice of ARV regimen in HBV/HIV co-infected individuals

- ART regimen containing two agents that are also active against HBV, thereby preventing the selection of HIV and HBV resistant mutants
- TDF and Lamivudine/Emtricitabine and Efavirenz as a fixed drug combination is first line therapy for adults, adolescents and children older than three years
- TDF, TAF, Lamivudine or Entecavir should not be used as single agents

d) outcomes after five years of FDC therapy (TDF, Laminvudine/Emtricitabine and EFV)

HBeAg-positive patients have high rates of: [104,105]

- HBV DNA suppression (90 per cent)
- HBeAg loss (46 per cent)
- HBsAg loss (12 per cent)
- no evidence of resistance
- reduced progression to cirrhosis
- risk of HCC persists, but is low

There was no significant difference in response rates compared with HBV mono-infection:

- HIV treatment regimens that exclude Tenofovir may lead to flares of HBV due to ART-associated IRIS

- treatment discontinuaion, especially Lamivudine, is associated with HBV reactivation, ALT flares and hepatic decompensation
- if ARVs need to be changed because of HIV drug resistance or toxicity, then TDF and Lamivudine or TDF/Emtricitabine should be continued together with the new ARV drugs

e) monitoring of FDC

- recommend serum creatinine at baseline, three, six and 12 months and then annual renal function assessment
- more frequently if high risk for renal dysfunction
- HIV-associated nephropathy:
  - Tenofovir Alafenamide can be accessed via a Section 21 application to SAHPRA
  - consider Entecavir as part of ART regimen, provided no previous exposure to Lamivudine or no evidence of Lamivudine-associated HBV plymerase resistance
- consider annual assessment of bone function:
  - TDF in children of 12 years and older and weighing at least 35kg

5.19.7 Extrahepatic disease

Patients with chronic HBV and active HBV replication who present with extrahepatic disease (vasculitis, polyarteritis nodosa, glomerulonephritis, purpura, arthralgias and peripheral neuropathy) should receive NUC therapy, but efficacy is variable:

- Lamivudine has been most widely used, but TDF, TAF or Entecavir are now preferable and the NUC depends on the renal function
- Plasmapheresis and steroids, in combination with a NUC, have been used in the initial phases of extrahepatic disease
- Interferon-based therapy may worsen immune-mediated extrahepatic manifestations

5.19.8 Liver transplant recipients

Recurrent HBV infection occurs in 70 to 90 per cent of HBsAg-positive recipients without immunoprophylaxis.[106] Patients with high serum HBV DNA levels and HBeAg-positivity at the time of liver transplantation have the highest rate of recurrence post-transplantation, with a corresponding decrease in patient and graft survival. [107-109]

a) pre-transplant management

- antiretroviral therapy given before transplantation aims to reduce serum HBV DNA to low or undetectable levels[110-113]
  - this may delay or even prevent the need for transplantation
- TDF, TAF and Entecavir are the preferred NUCs for patients undergoing liver transplantation for end-stage liver disease or HCC. [33,34] NUC choice is determined by renal function and previous exposre to Lamivudine
- Lamivudine improves liver function, reduces fibrosis and decreases risk of HCC in pre-transplant patients[114-117]
  - significant risk of drug resistance
  - can be used in clinically unstable patients with decompensated cirrhosis or acute liver failure as the risk of resistance is not immediate (20 per cent at six months)

b) post-transplant management

- NUC therapy in combination wiithh HBIG is recommended to prevent HBV recurrence118,119
- Lamivudine has been used in combination with HBIG
- reduced the risk of recurrent HBV at three years post transplant to less than ten per cent
- Entecavir or TDF or TAF or combination NUC therapy (Lamivudine and TDF or TDF/Emtricitabine) is now recommended together with HBIG
- the optimum dosage, mode of administration (IVI or IMI) and duration of HBIG therapy in combination with potent NUCs is not yet established[121]
- life-long antiviral therapy to prevent recurrent HBV is required

5.19.9 Management of patients receiving anti-HB IgG core antibody positive donor livers:

- overall risk of de novo HBV infection is reported to be as high as 75 per cent120-122 depending on the HBV immune status of the recipient
- the risk is particularly high in endemic countries such as South Africa, where these donors often have occult HBV
- in the absence of HBV prophylaxis, risk of de novo HBV[123,124]
  - 58 per cent in HBV non-immune individuals

- 18 per cent in previously vaccinated individulas with protective anti-HBs titres
- 14 per cent in isolated anti-HB IgG core positive individuals
- four per cent in naturally immune individuals – anti-HBs and anti-HB IgG core positive

- liver grafts from anti-HB IgG core positive donors can be safely used[125]
  - preferentially in HBsAg-positive or anti-HBc/ anti-HBs-positive recipients
  - non-immune HBsAg-negative recipients should receive Lamivudine prophylaxis
  - anti-HB IgG core and anti-HBs-positive recipients may not need prophylaxis
- Lamivudine is recommended as the most cost effective treatment option to prevent de novo HBV125
- HBV hhyperimmunoglobulin (HBIG) is not required[125]
- lifel-ong antiviral therapy is recommended in recipients with:
  - no immunity or vaccine-induced immunity, but not in liver recipients with natural immunity (IgG anti-HBc and anti-HBs positive)[125]

5.19.10 Management of transplant recipients of non-hepatic organs from donors who are HBsAg-negative and anti-HB IgG core antibody positive:

- reported risk of de novo HBV in HBV non-immune kidney transplant recipients ranges from 0 to 27 per cent126
- three per cent risk of de novo HBV has been reported in HBV non-immune cardiac recpients127
- risk of transmission varies depending on HBV DNA level, immunisation status and antiviral therapy
- anti-HB IgG core positive grafts should ideally be given to a HBV immune recipient (anti-HBs >10mIU/ml) if the recipient is HBV seronegative, antiviral therapy should be given to prevent de novo HBV, especially if donor has detectable HBV DNA
- optimal duration of prophylactic antiviral therapy is not known
- Lamivudine is recommended for one year in HBV seronegative non-liver transplant recipients
- anti-viral prophylaxis is not recommended in HBV-immune non-liver transplant recipients
- HBV hyperimmunoglobulin (HBIG) is not required

5.20 General Measures for HBV Control:

- introduction of the HBV birth dose vaccine as part of the EPI vaccination schedule in 2019 to reduce MTCT
- prevention of exposure through the use of standard infection precautions amongst HCWs
- screening of blood, blood products and organs for HBV
- implementation of rigorous infection control procedures for haemodialysis patients
- introduction of needle exchange programmes and opiate substitution for injecting drug users to reduce the spread of HBV, HCV and HIV
- advice on ethanol intake: more than 20 g/day in women and more than 40 g/day in men is associated with an increased risk of development of cirrhosis[128,129]

5.20.1 Management of HBsAg-positive persons to reduce the risk of secondary transmission:

- refer HBsAg-positive individuals for clinical assessment and management
- active counseling:
  - risk of transmission to infants and household, sexual and needle sharing contacts
  - cannot donate blood, plasma, tissue, ova or semen
  - avoid sharing household items that may be contaminated with blood such as toothbrushes, razors, hairclippers, nail-grooming equipment, etc
  - inform their dentist of their HBV status

  all household, sexual and needle-sharing contacts should be identified and tested for susceptibility to HBV infection (HBsAg, anti-HBs, IgG anti-HBc)
- identified susceptible non-immune contacts should be vaccinated against HBV
  sexual partners should be counselled to use barrier methods such as condoms to prevent exposure to sexual fluids until they have documented protective anti-HBs titres

5.21 Role of HBV Vaccine in the Control of HBV

HBV and its associated complications is an entirely vaccine preventable disease:[130]

- HBV vaccines are produced by recombinant DNA technology or are plasma-derived
- both formulations are safe and do not transmit HBV, HCV or HIV
- plasma-derived vaccines are thought to be more immunogenic
- combined HAV and HBV vaccines are available
- vaccine stored at two to eight degrees Celcius, but is thermostabile outside the cold chain [131,132]
- dosing schedules depend on:
  - type of vaccine
  - age of administration
  - need for rapid immunisation
  - previous non-response to HBV immunisation
- usual HBV vaccine dosage:
  - 20mcg/ml IMI into deltoid mucscle in adults
  - 10mcg/0,5ml IMI into anterolateral aspect of the thigh in neonates and infants
- three-dose series administered at birth, one and six months produces a protective anti-HBs response in:
  - 30 to 55 per cent of healthy adults aged 40 years or younger after the first dose
  - 75 per cent after the second dose
  - more than 90 per cent after the third dose
- these response rates decline when the vaccine is given to older individuals
  - less than 90 per cent in persons older than 40 years

  75 per cent in those older than 60 years
- alternative immunisation schedules: birth, one and four months or birth, two and four months or birth,one, two and 12 months
  - similar rates of protection as those described above
  - useful schedule in travelers who present at least two months before departure
  - ensures better compliance with completion of the immunisation schedule
- host factors (e.g. age, smoking, obesity, cirrhosis, genetic factors, immune suppression, renal failure, etc.) result in a decreased vaccine response

5.21.1 HBV immunisation in the EPI

- April 1995: HBV immunisation was incorporated into the South African EPI schedule
  - DtaP-IPV/Hib + HBV is given at six, 10 and 14 weeks of age and a booster at 18 months
- if a hexavalent vaccine is given according to the EPI schedule (six, 10 and 14 weeks), then a HBV monovalent vaccine birth dose is recommended for improved immunogenicity and protection against perinatal vertical transmission
- 2019: HBV monovalent birth dose vaccine to be introduced: Should be given at the same time as the oral polio and BCG to prevent perinatal transmission any child, who has missed any HBV immunisation dose, should receive the necessary catch-up doses, with four-week periods between doses until all doses are received for age
- 2020: HBV monovalent birth dose vaccine to be introduced: Should be given at the same time as the oral polio and BCG to prevent perinatal transmission

5.21.2 Pre-exposure immunisation of non-immunised infants, adolescents and adults

a) individuals recommended to receive pre-exposure HBV immunisation: [130,133,134]

- infants and adolescents not previously immunised who should have received routine immunisation through the EPI (catch-up immunisation)
- persons at risk for infection by percutaneous or mucosal exposure to blood/body fluids or by sexual exposure or at increased risk of severe illness if infected with HBV:
  - healthcare workers, student healthcare workers and workers in healthcare facilities with reasonable anticipated risk for exposure to blood or blood-contaminated body fluids- all laboratory workers working with clinical speciments
  - workers and residents of facilities for the developmentally disabled with a high risk of HBsAg-positive residents with aggressive

behaviour or special medical problems which increase the risk of HBV exposure

- workers and residents of correctional service facilities
- members of the police, firefighters and members of the armed forces
- household contacts of HBsAg-positive persons
- sex partners of HBsAg-posivite persons
- persons who inject or use drugs
- men who have sex with men
- persons seeking evaluation for treatment of a sexually transmitted disease
- patients receiving frequent transfusions of blood or blood components
- persons with endstage renal disease requiring dialysis
- transplant candidates before transplantation
- persons with chronic liver disease
- persons with HIV infection
- all other persons seeking protection from HBV infection, including travelers

b) post-immunisation testing for immunity:

- up to ten per cent of healthy adults receiving three doses of the HBV vaccine according to the recommended schedule may not develop protective anti-HBs ≥10 mIU/ml
- routine post-immunisation anti-HBs testing for immune response to immunisation is recommended
- post-immunisation anti-HBs testing is recommended in high-risk individuals:
  - high-risk healthcare workers
  - sex and needle sharing partners of HBsAg-positive individuals
  - household contacts of HBsAg-positive persons
  - HIV-infected individuals
  - haemodialysis patients
  - individuals with chronic liver disease
  - MSM
  - immuno-compromised individuals

c) re-immunisation in adults:

- persons who do not respond to a primary immunisation schedule should be offered re-immunisation with three doses of HBV vaccine, one month apart
- re-immunisation gives rise to protective anti-HBs titres:
  - 25 to 50 per cent of non-responders with a single additional dose
  - 44 to 100 per cent with a three-dose re-immunisation series
- individuals who do not develop protective anti-HBs titres one to two months after re-immunisation may be:
  - primary non-responders
  - infected with HBV and should be tested for HBsAg
- repeat immunisation (nil, one and two months with a six-month booster) with double the standard dose has been demonstrated to enhance the re-immunisation response in one study, but not in another[133,134]
- individuals who do not respond to HBV immunisation should be given HBV Immunoglobulin (HBIG) as post-exposure prophylaxis (PEP) following HBV exposure

5.21.3 HBV immunisation of haemodialysis and immuno-compromised patients:

- patients with pre-endstage renal disease, ideally before they become dialysis dependent
- patients with endstage renal disease requiring haemodialysis or peritoneal dialysis[135]
- higher HBV vaccine doses recommended: Adult haemodialysis or peritoneal dialysis patients

- four doses of HBV vaccine containing 40µg HBsAg at nil, one, two and six months [134]
- limited data on immune response of paediatric patients on haemodialysis

- protective anti-HBs titres achieved in 75 to 97 per cent of children receiving higher dosages (20µg HBsAg) in a three- or four-dose schedule
- anti-HBs testing recommended after final dose of HBV vaccine series to determine the need for re-immunisation
- haemodialysis patients: Annual testing of anti-HBs titres with booster doses if titre is less than 10 mIU/ml
- immuno-compromised patients (HIV infection, diabetics, individuals on immunosuppression or receiving chemotherapy):

- reduced humoral response to HBV immunisation
- modified dosing regimens, including doubling the dose or administering additional doses may increase response, but evidence is limited to support these schedules

5.22 Prep for HIV in setting of HBsAg-Positivity

Pre-exposure prophylaxis (PrEP) is the use of Tenofovir and Emtricitabine/Lamivudine preferably as a combination pill by HIV-negative individuals before potential exposure to HIV to prevent them from acquiring HIV infection. Consult the most recent national Department of Health Guideline for PrEP eligibility criteria.

PrEP should be used as part of a package including condoms, lubricants for anal sex, STI management, screening and management of intimate partner violence, sexual and reproductive health services, medical male circumcision and HIV services, including counseling and testing, HIV management, ART, PEP, and PrEP:

- it is essential to test for HBsAg and HBsAb to diagnose HBV-infected individuals as well as to identify those in need of HBV immunisation
- if HBsAg positive, do ALT and decide on need for long-term NUC therapy
- if ALT persistently elevated or other abnormal liver function tests, refer for assessment for long-term NUC therapy
- it is is safe to initiate PrEP in the setting of acute and chronic HBV
- PrEP users with chronic HBV infection who develop abnormal liver function tests should be referred for assessment
- if PrEP is stopped, monitor ALT every three months

Discontinuation of Tenofovir and Emtricitabine/Lamivudine in patients with HBV requires referral to a specialist because of a risk of a hepatitis flare.

5.23 Post-Exposure Prophylaxis (Pep) Against HBV

5.23.1 Indications for PEP

PEP is indicated following exposure to blood or body fluids of a known or potential HBsAg-positive source if the exposed individual does not have protective anti-HBs ≥10 mIU/ml or if anti-HBs status is unknown and testing will delay administration of HBV immunisation or HBIG.

Exposures in which HBV PEP should be given include:

- ercutaneous (e.g. bite or needlestick) or mucosal exposure to blood or body fluids of a known or potential HBsAg-positive source
- neonates born to HBV-infected women
- sex or needle sharing contact of a HBsAg-positive person or a person of unknown HBsAg status
- victims of sexual assault/abuse by a perpetrator who is HBsAg-positive or of unknown HBsAg status

5.23.2 Effectiveness of PEP:

- a combination of HBIG and active HBV immunisation is highly effective in preventing transmission after exposure to HBV
- HBIG provides passively acquired anti-HBs which is immediately protective and lasts for three to six months
- HBIG is approximately 75 per cent effective in preventing clinical HBV infection if administered soon after HBV exposure
- HBIG alone does not confer long-lasting protection against HBV
- HBIG is the primary means of protection of non-responders to immunisation

5.23.3 Timing of PEP:

- the most important determinant of PEP effectiveness is the timing of administration of HBIG and the first HBV vaccine dose
- PEP effectiveness decreases with increasing delay in administration following exposure and is unlikely to be effective:

- more than seven days after perinatal and needle stick exposures
- more than 14 days after sexual exposure

5.23.4 PEP for babies born to HBV-infected women

Perinatal transmission usually occurs at birth and is a risk for any baby born to an HBsAg-positive woman. The risk is highest from mothers with HBeAg-positivity or if the HBV DNA is more than 200 000 IU/ml.

Screening pregnant women for HBsAg is essential in order to timeously administer PEP to babies born to HBsAg-positive women:

- neonates born to HBsAg-positive mothers should receive 0.5 ml (200 IU) HBIG and HBV monovalent vaccine within the first 24 hours, but preferably within 12 hours of delivery at different injection sites (anterolateral thigh)
- probably remains protective if administered up to 72 hours after exposure

thereafter, the same immunisation schedule is followed as for other infants, with the additional HBV vaccine doses given at six, 10 and 14 weeks of age either as a monovalent vaccine or as a component of the hexavalent vaccine

- the combination of HBIG and HBV immunisation is 95 per cent effective in preventing MTCT
- HBIG is expensive and not readily available
- pregnant mothers with HBV DNA of more than 200 000 IU/ml should receive Tenofovir at 28 to 32 weeks to further reduce the risk of MTCT and continue for 12 weeks after delivery
- children born to HBsAg-positive mothers should be offered post-immunisation testing for HBsAg and anti-HBs at nine to 18 months of age
- children with anti-HBs of 10 mIU/ml or more are protected and need no further management
- children who have anti-HBs of less than 10mIU/ml should be given a second course of immunisation as they may be at risk of exposure in the household
- children who are HBsAg-positive should be referred for clinical management

5.23.5 PEP for HBV in the healthcare setting

a) pre-exposure measures:

- routine pre-exposure HBV immunisation must be provided to all HCWs, including laboratory and cleaning workers who may perform tasks involving contact with blood, blood-contaminated body fluids or sharps
- pre-immunisation screening for HBV infection is not necessary unless the healthcare facility finds this to be cost-effective
- post-immunisation anti-HBs testing should be performed one month after completion of the immunisation schedule
  - if non-immune, consider screening for HBsAg and if negative, re-immunise
- administration of HBV vaccine doses to workers should be recorded in his/her workers file
- standard infection control precautions should be implemented at all times

b) post-expose management: (see Table 13)

- exposure should be reported according to standard procedures for the institution
- wounds should be washed with soap and water and mucous membranes should be flushed with water
- exposure should be evaluated for the potential to transmit HBV
- establish HBsAg status of the source patient and HCW
- if HBsAg source status is not obtainable, the HCW should be managed as if source individual is HBV infected
- establish anti-HBs status of HCW

Table 13: Recommendations for PEP: Occupational exposure to HBV[136]

Immunisation and anti-HBs status of exposed HCW*	Management		
	Source HBsAg-positive	Source HBsAg-negative	Source unknown or unavailable for testing
Unvaccinated	• HBIG and initiate HBV vaccine series	• initiate HBV vaccine series	• HBIG and initiate HBV vaccine series
Previously immunised			
Known responder**	• no action	• no action	• no action
Known non-responder***	• HBIG and initiate HBV re-immunisation (if not previously attempted) • repeat HBIG at one month	• re-immunisation (if not previously been attempted)	• HBIG and initiate HBV re-immunisation (if not previously attempted) • repeat HBIG at one month
Anti-HBs response unknown	Test exposed person for anti-HBs: • if anti-HBs positive: no action • if anti-HBs negative: Administer HBIG and HBV vaccine booster and re-check titre in one month	Test exposed person for anti-HBs: • if anti-HBs positive: no action • if anti-HBs negative: HBV vaccine booster and re-check titre in one month	Test exposed person for anti-HBs (if the delay is more than 24 hours treat as known non-responder): • if anti-HBs positive: no action • if anti-HBs negative: HBIG and HBV vaccine booster and re-check titre in one month

HCW: Healthcare worker: Test for HBsAg and anti-HBs status
HBIG: Dose is 0.06ml/kg (500 IU) intramuscularly
*If HCW is known to be previously HBV-infected, they cannot be re-infected and do not require PEP
**A responder is an individual who developed adequate anti-HBs titres (≥10mIU/ml) following immunisation
***A non-responder is an individual who developed inadequate anti-HBs titres (<10mIU/ml) following immunisation
HBIG and first dose of HB vaccine should be given at the same time at different sites

5.23.6 PEP for sexual exposure to HBV align with PEP guidelines 2016:

- victims of sexual assault should receive comprehensive investigation and management as per the National Management Guidelines for Sexual Assault Care and National Sexual Assault Policy 2005[137]
- HBV is transmitted sexually, but the risk of transmission per exposure is unclear
- HBV vaccine must be administered to all sexual assault victims who are not already fully immunised
- HBIG must be considered in high-risk exposures due to the increased protection afforded by a PEP regimen combining HBV vaccine and HBIG
- the HBV vaccine should be given in three doses immediately and at one and two months
- HBsAg of the exposed individual should be performed at baseline, 12 and 24 weeks
- if the individual is found to be HBsAg-positive at baseline, the vaccine schedule can be discontinued
- HBIG is approximately 75 per cent effective in preventing acute or chronic HBV infection following sexual exposure if given within seven days of exposure, but should not be used alone unless HBV vaccine is unavailable as it does not afford long-lasting protection
- victims of sexual assault must be screened for HIV, HCV and other sexually transmitted diseases

5.23.7 PEP in other situations

HBV exposure may occur in situations other than in the setting of perinatal, sexual or occupational exposure in the healthcare setting.

Such situations include exposure following wounds such as human bites, exposure in the situation of mass casualty events or exposure following needle sharing. The PEP recommendations in these situations are the same as for occupational exposure.

The principles of management of such exposures are similar to those described in paragraph 5.23.6 and include:

- establish HBsAg status of source individual and the exposed individual
- establish the anti-HBs status of the exposed individual
- unknown HBV status of the exposed individual: HBsAg and anti-HBs should be performed at baseline
- exposed individual is HBsAg-positive at baseline: HBV vaccine schedule can be discontinued
- individuals with documented completion of HBV immunisation schedule who did not receive post immunisation testing should receive a booster dose of vaccine at the time of exposureif the source is HBsAg-positive or unknown: HBV vaccine and HBIG should be given

5.24 Diagnostic, prevention and Treatment Options: Primary, Secondary and Tertiary Levels of care

5.24.1 Diagnosis:

- all levels of care: Viral serology (HBsAg, anti-HBs, HBeAg, anti-HBe, IgG and IgM anti-HB core), HBV DNA quantification with gene expert technology
- secondary and tertiary level care: HBV DNA quantification
- tertiary level care: HBV genotype and HBV resistance testing

5.24.2 Assessment of clinical severity:

- all levels of care: FBC, INR, serum creatinine and liver profile; enables APRI scoring to assess for cirrhosis and choice of NUC
- secondary and tertiary levels of care: Ultrasound liver ± mobile fibroscan
- tertiary level care: Fibroscan and liver biopsy

5.24.3 Treatment:

- acute HBV:
  - uncomplicated cases: Managed at primary level care including screening at six months to exclude progression to chronic HBV
  - complicated cases with synthetic dysfunction: Refer to secondary level care
  - fulminant hepatitis: Refer to tertiary level care
- chronic HBV
  - HBeAg-negative chronic HBV infection (immune control): Follow up at primary level care
  - HBeAg-positive chronic HBV infection (immune tolerant): Follow up at primary level care
  - hepatitis BeAg-positive chronic HBV (immune clearance): Secondary and tertiary level care with option of down-referral to primary level care when stable on therapy
  - hepatitis BeAg-negative chronic HBV (immune escape): Secondary and tertiary level care with option of down-referral to primary level care when stable on therapy
  - cirrhotics (compensated and decompensated): Tertiary level care
- HIV/HBV co-infection:
  - primary level of care, unless abnormal LFTs, then referral to secondary level care.
  - cirrhotics managed at tertiary level care
- HBV/HCV and HBV/HCV/HIV co-infection:
  - tertiary level care and with option of down-referral to primary level care, once HCV successfully treated and stable on NUC or ARV therapy

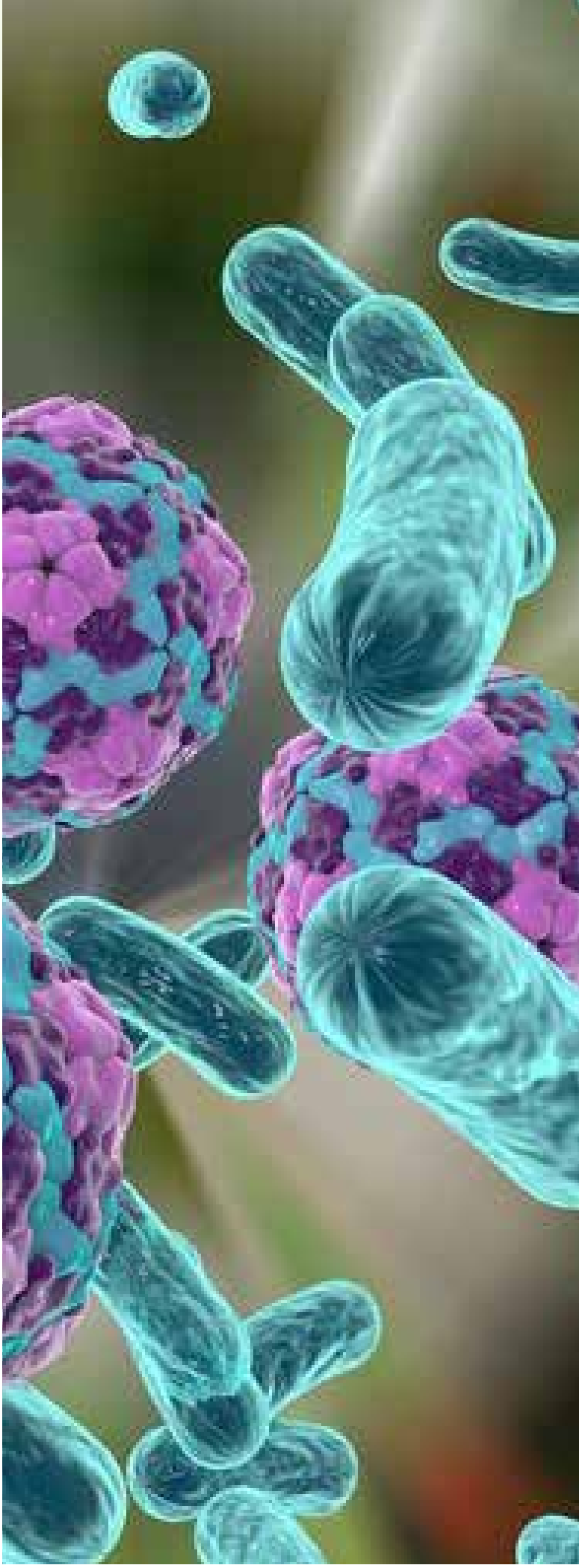
5.24.4 Therapeutic options:

- Lamivudine and TDF: All levels of care for both HBV mono-infected and HBV/HIV co-infected individuals
- Entecavir, TAF and Pegylated Interferon: Tertiary level care

5.24.5 Prophylaxis:

- all levels of care:
  - screening of contacts: HBsAg, anti-HBs and IgG anti-HBc
  - HBV immunisation and HBIG

ENTER YOUR PATIENT CHARACTERISTICS FOR INSTANT GUIDANCE ON MANAGEMENT CLINICALOPTIONS.COM/HEPBCONSULT



HEPATITIS C (HCV)

CHAPTER 6

6.1 Introduction

Globally, 71 million people are viremic for HCV infection[1,2]. About 15 to 25per cent of infected individuals spontaneously clear the virus within six months of infection. However, the remaining 75 to 85 per cent will develop chronic HCV3. Of those chronically infected, the risk of cirrhosis is 15 to 30 per cent within 20 years with a one to four per cent per annum risk of hepatocellular carcinoma[3].

HCV epidemiology in South African is poorly understood and characterised. An estimated 600 000 South Africans (95 per cent UI 400 000 – 800 000) are chronically infected. Previous data suggests a seroprevalence in urban blood donors (low risk) of 0.01 - 2.6 per cent, with a higher rate in the rural population (3.8 per cent)[4]. Seroprevalence rates are higher in high-risk groups with recent data suggesting almost 50 per cent of PWID and three to six per cent of MSM, especially if HIV positive, are HCV infected. With PWID, there is significant regional variation in viremic prevalence, highest in Pretoria (~75 per cent) and between 30 and 40 per cent in Durban and Cape Town [5,6].

6.2 Hepatitis C Genotypes

HCV is a linear, single-stranded, positive-sense RNA virus belonging to the Flaviviridae family and has no polymerase proofreading ability, producing heterogeneous viral populations or quasispecies. There are six clinically relevant HCV genotypes and more than 80 subtypes. Genotype prevalence varies according to geographic region and route of acquisition [7-8]. South Africa is a “pan-genotypic” country with genotypes 1 to 5 being observed, however genotype 1 and 5 are predominant with genotype 4 being detected with increasing frequency. Genotype 5a, first identified in South Africa, is a genotype unique to South Africa[9-12]. Viral genotype is a strong determinant of responsiveness to Interferon/ Ribavirin based combination therapy, but not with the newer DAAs. In PWID, genotype 1a (73 per cent) and 3a (15 per cent), predominated.

6.3 Transmission of Hcv

HCV remains viable on environmental surfaces at room temperature for at least 16 hours, but typically no longer than four days, ,13,14 and transmission occurs via parenteral and non-parenteral routes.Ten to 40 per cent of HCV-infected individuals have no clear identifiable risk factor.

6.3.1 Parenteral transmission:

- HCV is most efficiently transmitted through parenteral inoculation:
  - predominant risk is in PWID through the sharing of syringes and needles15
  - risk is as high as 90 per cent after five years in PWID
  - tattooing, body piercing, traditional scarification or circumcision
  - needle-stick injuries

6.3.2 Non-parenteral transmission:

This is less well defined and includes:

- sexual transmission:
  - infrequent in heterosexual couples 16,17
  - HIV-infected heterosexual partners of HCV-infected individuals
  - high-risk behaviour sexual practices
  - MSM, especially if HIV positive16-19
- MTCT: 20-22
  - two to four per cent of infants born to HCV-infected women
  - certical transmission risk increases to 10.8 to 25 per cent in HIV/HCV co-infected mothers

6.3.3 Household transmission:

- percutaneous/mucosal exposure to blood and sharing of contaminated personal items such as razors, toothbrushes, nail-grooming equipment is described, but uncommon.[23,24]

The typical routes of transmission occur in South Africa with previous or current injecting drug use and blood/blood products before 1992 being most prevalent. However, the extent to which tattooing, body piercing and in particular traditional practices play a role, are unclear. Universal infectious precaution principles through maintaining clean, aseptic techniques and disinfection procedures in healthcare facilities, are important in preventing nosocomial transmission.

6.4 Groups at Risk for Hcv

Individuals at higher risk for CV infection include:

- PWID
- recipients of blood, blood products and solid organ transplants before 1992
- unsafe medical injection practices
- occupational exposure e.g. HCWs with needle stick injuries
- chronic haemodialysis (up to 10 per cent risk)
- high-risk/traumatic sexual practices
- MSM
- use of intranasal cocaine
- tattoos, body piercing, acupuncture
- surgical procedures, including dental/orthodontic procedures without proper sterilisation procedures
- traditional/cultural practices e.g. circumcision, scarification rituals

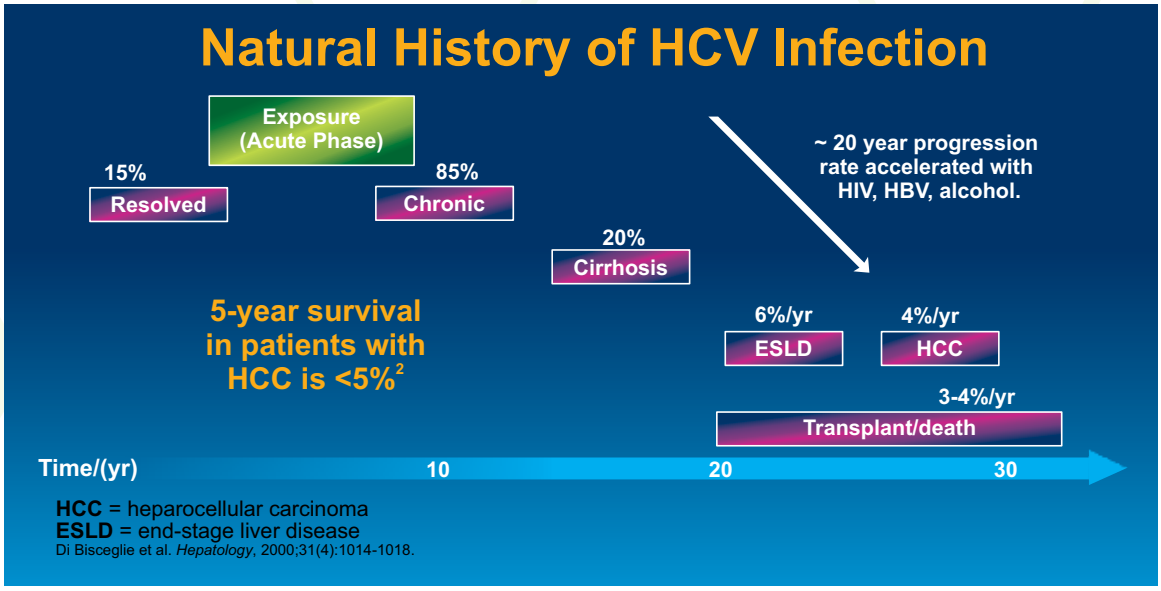
6.5 Clinical Presentation of Hcv

Variation in disease progression is characteristic of HCV infection and contributing factors include environmental, host genetic and immunological factors. Several factors including alcohol, HIV or HBV co-infection, iron overload states and obesity accelerate the clinical course of chronic HCV infection. HCV viral load or genotype does not influence the clinical course.

After the initial infection, HCV usually has an incubation period of four to 16 weeks. Most individuals who develop acute HCV are completely asymptomatic25. Jaundice is uncommon and fulminant liver failure complicating acute HCV infection is rare. Anti-HCV antibodies can take 12 to 16 weeks, from the time of first infection to develop. However, HCV RNA is detectable in serum as early as one to three weeks after exposure. The persistence of HCV RNA beyond 24 weeks after acute infection marks the onset of chronic infection. The natural history of chronic infection is long and typically exceeds 20 years. Up to 25 per cent will develop progressive chronic liver disease and progress to cirrhosis and endstage liver disease. Once cirrhotic, the risk of hepatocellular carcinoma is one to four per cent per annum. Individuals are usually asymptomatic until presentation with complications of cirrhosis25.

6.5.1 Natural history:

Figure 3: Natural history of HCV infection



6.6 Extrahepatic Manifestations of Hcv

HCV has been associated with several extrahepatic manifestations:

- autoimmune (e.g. Sjögren's syndrome, cryoglobulinaemia, polyarteritis nodosa)
- porphyria cutanea tarda
- lymphoproliferative diseases (e.g. B-cell non-Hodgkin's lymphoma)
- insulin resistance: Progressive insulin resistance, impaired fasting glucose (IFG) and/or type 2 diabetes mellitus (DM) are higher in chronic HCV patients (50per cent) than in the general population (14.5 per cent)[26]
- neurocognitive dysfunction

6.7 HIV/HCV Co-Infection

Documented HIV/HCV co-infection prevalence in South Africa ranges from one to 13.4 per cent and three to six per cent in MSM 27. HIV co-infection significantly alters the natural history of HCV 28-333 and is regarded as a priority for HCV treatment with DAAs given that there is:

- accelerated fibrosis and progression to cirrhosis
- increased hepatocellular carcinoma risk
- increased HCV infectivity risk, especially MTCT of HCV
- increased risk of ART and TB drug-induced liver injuries
- reduced response to interferon-based therapy

6.8 Diagnosis of HCV

- anti-HCV (EIA-antibody)
  - more than 95 per cent sensitivity
  - detects anti-HCV antibodies in 80 per cent infected individuals within six weeks of primary infection
  - screening test of choice:
- ELISA in a central laboratory
- RDT: Point-of-care anti-HCV using blood or saliva (more than 95 per cent sensitive and specific (positive predictive values more than 99 per cent and negative predictive values more than 95 per cent) in a local study

There are two WHO pre-qualified RDTs Test Kits:

- quantitative HCV PCR (viral load quantification):
  - mandatory if HCV EIA or RDT-positive - confirms active viraemia and is the preferred HCV PCR option

- Xpert HCV is WHO pre-qualified HCV quanitification platform – assays available for both serum and fingerprick blood with desktop point-of-care s available
- central laboratories provide strong support – can utilise Roche Cobas Amplicor, Cepheid Xpert

- genotype testing
  - required to assist in choosing DAA treatment regimens - with pangenotypic DAA therapies this may not be required – genotyping to remain central laboratory function
- resistance associated substitution testing
  - for treatment failures (provided by a national centre) - managed at tertiary level care

6.9 Pre-Treatment Clinical Evaluation

6.9.1 Medical evaluation includes:

- clinical history and physical examination
- assessment of the liver disease:
  - liver profile: total bilirubin, conjugated bilirubin, albumin, ALT, AST, ALP, GGT
  - FBC and differential count
  - INR to assess synthetic function
  - fibrosis assessment: see 6.9.2
- assessment for other co-factors that accelerate fibrosis progression:
  - viral co-infection: HIV, HBV
  - alcohol use
  - non-alcoholic fatty liver disease
  - iron overload
  - drug/toxin-induced liver injury
- HBV and HAV serology to assess need for immunisation:
  - anti-HAV IgG negative: Needs HAV immunisation
  - HBsAg, anti-HBs and IgG HBcore negative: Needs HBV immunisation
- HCC screening: Alpha fetoprotein and ultrasound of the liver (six-monthly) if cirrhosis present even after SVR

6.9.2 Assessment of fibrosis

Assessing the degree of fibrosis remains an important aspect of management as it determines prioritisation and duration of therapy:

a) histological assessment

Liver biopsy remains the golden standard for the assessment of fibrosis[34,35] as well as the contribution of ancillary pathology, e.g. steatosis, iron overload, alcohol and DILI.

b) non-invasive assessment for fibrosis - preferred option for rapid linkage to care

- serum-based markers: APRI (platelets and AST) score; FIB-4 (age, ALT, AST, platelets) [36]
- vibration controlled transient elastography (VCTE): FibroScan©: Measures liver stiffness through doppler pulse ultrasound[37,38]

Non-invasive techniques have excellent utility for the identification of HCV-related cirrhosis. Serum markers are less accurate at earlier disease stages, whilst VCTE has a better predictive value for milder (F0, F1) and more severe fibrosis (≥F3) and slightly less so for mid-range fibrosis.

6.10 Treatment of HCV39-41

All patients with HCV must be offered therapy unless concomitant co-morbidities will result in short-term mortality.

6.10.1 Acute HCV:

- diagnosing suspected acute HCV is clinically challenging and tertiary level referral is strongly advised
- regular laboratory monitoring is recommended in the setting of acute HCV
- if a decision has been made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is recommended to allow for spontaneous clearance
  - usually in setting of high risk for ongoing transmission: PWID and MSM
- if a delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of six months

The same DAA regimens that are recommended for chronic HCV infection are recommended for acute infection - shorter durations of treatment are acceptable (eight weeks), but ideal timing of DAA initiation have not yet been established.

6.10.2 Chronic HCV

The aim of treatment is to achieve a SVR that results in:

- reduced necro-inflammation and progression to fibrosis, cirrhosis and endstage liver disease
- reduction in risk of HCC
- improved liver-related morbidity and mortality
- improved all-cause mortality
- prevents onward transmission

6.10.3 Treatment prioritisation i.e. patients who need to be treated first when the national programme is initiated:

- significant fibrosis (F3) or F4/cirrhosis (including compensated cirrhosis)
- HIV or HBV co-infection
- extrahepatic manifestations
- acute HCV
- liver transplant and other solid organ transplant recipients
- PWID

6.11 HCV Treatment Options

All HCV-infected patients should receive general counselling about the disease and must be referred for treatment to a treatment facility or centre experienced in managing HCV. PWID must receive additional harm reduction support.

Table 14: Definitions of terms used to evaluate response to HCV treatment

Term	Explanation
Sustained virological response (SVR)** • DAA-based therapy	• Undetectable HCV RNA at least 12 weeks after the end of DAA therapy
SVR is associated with a significant improvement in liver-related and all-cause morbidity and mortality and improved quality of life	

**DAAs are currently not registered by SAHPRA. The process to obtain DAAs is to apply to the Drug and Therapetic Committee of the individual hospital for permission to use their budget for DAAs or for support to fund DAAs. Then apply for a SAHPRA Section 21 approval, and then arrange for generic DAA drugs to be supplied via India.

6.11.1 DAA therapy

The DAA regimens combine drugs from different classes that target multiple sites of the HCV life cycle. DAA combinations increase efficacy, decrease the risk of viral resistance and act synergistically to increase SVR.

The three main classes of DAAs are:

a) NS3/4A Protease Inhibitors (PI): Simeprevir, Grazoprevir, Voxilaprevir, Glecaprevir

- these PIs have a high potency, but a low barrier to resistance. Voxilaprevir and Glecaprevir are pangenotypic

b) NS5A inhibitors: Daclatasvir, Iedipasvir, Elbasvir, Velpatasvir, Pibrentasvir

- these DAAs have a very high potency, a low barrier to resistance and are mostly active against all genotypes, except Elbasvir and Iedipasvir

c) NS5B polymerase inhibitors: Sofosbuvir, Dasabuvir

- the nucleoside NS5B polymerase inhibitor, Sofosbuvir is the first in this class. It has intermediate potency with pangenotypic activity and a high barrier for resistance
- non-nucleoside polymerase inhibitors, including Dasabuvir have intermediate potency, a more limited genotypic activity and a low barrier to resistance

6.11.2 Current HCV treatment recommendations

Genotype		SOF-VEL	SOF-LDV	SOF-DCV3	GLE-PIB
Genotype 1a	Naive	12w	8w – 12w1	12w	8w
	Experienced	12w	12w2	12w	8w
Genotype 1b	Naive	12w	8w – 12w1	12w	8wk
	Experienced	12w	12w	12w	8w
Genotype 2	Naive	12w	No	12w	8w
	Experienced	12w	No	12w	8w
Genotype 3	Naive	12w	No	12w	8w
	Experienced	12w	No	12w	12w
Genotype 4	Naive	12w	12w	12w	8w
	Experienced	12w	12w2	12w	8w
Genotype 5	Naive	12w	12w	12w	8w
	Experienced	12w	12w2	12w	8w

Table 15: DAA regimens for non-cirrhotic treatment naive or experienced (including PEG-IFN/Ribavirin; PEG-IFN, or Sofosbuvir and Ribavirin) HCV mono-infected patients

SOF - Sofosbuvir; **VEL** - Velpatasvir; **LDV** - Ledipasvir; **DCV** - Daclatasvir; **GLE** - Glecaprevir; **PIB** - Pibrentasvir; **w** - weeks. Pangenotypic regimens are shaded. Ledipasvir active against GT1, 4, 5

1. eight weeks if HCV RNA is less than 6 000 000IU/ml, HIV-negative and non-black
2. requires addition of weight based dosed Ribavirin
3. as per WHO guidance; if treatment experienced consider addition of ribavirin

Genotype		SOF-VEL	SOF-LDV1	SOF-DCV2	GLE-PIB
Genotype 1a	Naive	12w	12w	12w	12w
	Experienced	12w	12w	12w	12w
Genotype 1b	Naive	12w	12w	12w	12w
	Experienced	12w	12w	12w	12w
Genotype 2	Naive	12w	No	12w	12w
	Experienced	12w	No	12w	12w
Genotype 3	Naive	12w	No	12w	12w
	Experienced	12w	No	12w	16w
Genotype 4	Naive	12w	12w	12w	12w
	Experienced	12w	12w	12w	12w
Genotype 5	Naive	12w	12w	12w	12w
	Experienced	12w	12w	12w	12w

Table 16: DAA regimens for compensated cirrhosis treatment naive or experienced (including PEG-IFN/ Ribavirin; PEG-IFN, or Sofosbuvir and Ribavirin) HCV mono-infected patients

SOF - Sofosbuvir; **VEL** - Velpatasvir; **LDV** - Ledipasvir; **DCV** - Daclatasvir; **GLE** - Glecaprevir; **PIB** - Pibrentasvir; **GZR** - Grazoprevir; **EBR** - Elbasvir; **w** - weeks. Pangenotypic regimens are shaded.

1. with compensated cirrhosis or treatment-experienced, consider adding weight based dosed Ribavirin
2. as per WHO guidance; consider add Ribavirin if compensated cirrhosis or treatment-experienced
3. if ribavirin intolerant, consider 24 weeks of SOF-LDV, SOF-DCV or SOF-VEL

DAAs are not as yet registered in South Africa. However, in the interim, DAAs are available via a SAHPRA Section 21 application process for named patients. Registration is anticipated in 2019 and beyond.

6.11.3 DAA treatment efficacy

SVR rates for DAA therapies exceed 90 per cent for all genotypes. Sofosbuvir/Velpatasvir, Sofosbuvir/Daclatasvir or Glecaprevir/Pibrentasvir offer a pan-genotypic option with SVR of 95 per cent or more. The presence of cirrhosis and previous treatment determines duration of treatment or need for Ribavirin, but no longer determines SVR. Individuals with stage 4 chronic kidney disease or on dialysis have been difficult to treat, but Glecaprevir/Pibrentasvir is effective and safe with SVR of 90per cent and more. If Glecaprevir/Pibrentasvir is unavailable, Sofosbuvir-based therapy must be dicussed with an expert. The major factor influencing DAA therapy is drug-drug interactions (especially with ARVs) that alter DAA efficacy through pharmacokinetic interactions as a result of enzyme induction or inhibition of the CYP P-450 enzyme subunits involved in the metabolism of DAAs. All potential drug-drug interactions must be checked before initiation of DAA therapy. https/:www.hep-druginteractions.org

6.11.4 Monitoring on DAA therapy

Patient monitoring is substantially simplified on DAA therapy as a result of the reduced side effect profile.

Recommended monitoring is as follows:

- baseline: FBC, Creatinine, liver profile, HCV RNA quantification
- week 4: FBC, INR, ALT, HCV RNA quantification
- week 8: FBC, differential (only if Ribavirin used)
- week 12 and 24: FBC, differential (only if Ribavirin used), Creatinine, limited liver profile, HCV RNA quantification (to assess EOT response)
- 12 weeks after EOT: Liver profile, HCV quantification (to assess for SVR)

If a patient has cirrhosis, monitor more frequently for decompensation.

6.12 Treatment of Special Populations

With the introduction of DAA therapy, there are now very few difficult-to-treat populations. Some populations require particular attention:

6.12.1 PWID

The WHO, United Nations Office on Drugs and Crime (UNODC), Joint United Nations Programme on HIV/AIDS (UNAIDS) and other normative agencies recommend treating PWID living with HCV infections using DAAs. Real work data on SVR among people with recent illegal drug use ranges between 95 per cent and 98per cent. Abstinance from ongoing use of illegal drugs is not a pre-requisite for DAA therapy, but counselling around potential risks of ongoing substance use and harm reduction is encouraged. Accessing HCV care and treatment within hospitals is challenging with community-based services with hepatologist support a proven and viable model for PWID with HCV mono-infection in locations with a high concentration of PWID. Treatment services should be accompanied by voluntary access to psychosocial services, sterile injecting equipment and opioid substitution therapy. DAA treatment should include counselling around potential re-infection, mechanisms to prevention infection and need for routine screening. Treatment approaches for PWID should take a public health approach and aim for rapid scale-up to enable treatment of PWID networks to reduce community viral load and risk of re-infection.

6.12.2 HCV/HIV co-infection

HIV co-infection significantly alters the natural history of HCV and is regarded as a priority for HCV treatment. In the PEG-IFN/RBV era of treatment, co-infection significantly and negatively influenced response rates. SVR rates for genotype 1 HCV were reduced to 30 to 40 per cent, whilst SVR rates were better for genotype 2 and 3. Only patients with a CD4>500mm^3 (either on ART or not) were eligible for therapy and cytopenias on therapy were significant. DAA therapy has completely altered therapeutic options for co-infected patients. Co-infection is no longer regarded as a “difficult to treat” population. SVR rates for co-infected patients are no different than that for HCV mono-infected patients. Treatment regimen recommendations for co-infection are the same as for HCV mono-infection. Drug-drug interactions need to be carefully assessed prior to selecting and initiating DAA therapy.

6.12.3 Decompensated liver disease

The ASTRAL-4 study showed that the combination of Sofosbuvir/Velpatasvir resulted in overall SVR rates of more than 90 per cent in patients with decompensated liver disease (Genotypes 1, 2, 3, 4 and 6).[42]

6.12.4 Treating children

Therapy has proven safe and effective in adolescents aged 12 to 17 years and weighing more than 35kg.43 Treatment duration is dependent on treatment history, genotype and cirrhosis. Data supports 12 weeks of Sofosbuvir-Ledipasvir for GT 1, 4, 5 and 6 and Sofosbuvir-Ribavirin for GT2 (12 weeks) or GT3 (24 weeks). The United States Food and Drug Administration (FDA) has recently approved Glecaprevir-Pibrentasvir for treatment of adolescents with GT1-6 with or without compensated cirrhosis.

6.12.5 Pregnancy

Ribavirin is teratogenic and is contraindicated during pregnancy. In addition, pregnancy should be avoided for six months after the end of Ribavirin-based therapy. The new DAA therapies are currently contraindicated during pregnancy. For now, women with HCV who wish to have children should either consider DAA therapy before pregnancy or defer treatment till after successful pregnancy. With effective short duration DAA therapy, the prior strategy is preferred. New, but very preliminary data suggests that DAA therapy in pregnancy may be safe, but more work is needed. Appropriate contraceptive measures should be used by women of childbearing age using Ribavirin or DAAs as well as the partners of men on therapy. Caesarean section does not reduce the risk of perinatal MTCT of HCV and instrumentation (e.g. foetal scalp monitoring, and forceps delivery) should be avoided as it increases the HCV transmission risk.

6.13 Primary Prevention and Control

There is no effective vaccine or immunoglobulin available for the prevention of HCV infection.

The major principles of prevention and control are to:

- reduce the number of new infections through prevention of transmission
- treat those who may transmit HCV e.g. PWID, MSM

Treatment with effective DAA therapy as a means of viral eradication has become a reality and may well reduce the need for a vaccine.

6.13.1 Blood and blood products:

- all blood and blood products are screened for HCV by the SANBS by EIA since 1991 and anti-HCV positivity is confirmed by NAT testing since 2005
- all plasma-derived products are subjected to virus inactivation
- all HCV-positive blood and blood products are removed from the pool of transfusion units
- disease transmission has been documented from HCV antibody-negative and PCR-negative blood units and for this reason blood products should only be used when necessary

6.13.2 HCW exposure:

- all HCWs must implement standard infection precautions and adhere to infection control practices at all times to limit and prevent infection of blood-borne infections including HCV, HBV and HIV
- reusable surgical and medical instruments must be adequately sterilised

Management of HCW following needle stick exposure to HCV: [44]

Risk of HCV acquisition following percutaneous exposure is 1.8 per cent (range nil to seven per cent), but rare from mucous membrane exposure. One study indicated that transmission only occurred following exposure to hollow bored needles:[42]

- establish HCV, HIV and HBV status of the source patient and HCW
- baseline testing of HCW within 48 hours of exposure (anti-HCV and HCV PCR and ALT) as well as screening for HBV and HIV
- frequency of follow up anti-HCV and HCV PCR testing depends on management objectives:
  - monthly testing if considering early initiation of treatment, otherwise at 12 and 24 weeks
- efficacy of DAA therapy is the same as for chronic HCV infection, although timing of treatment not yet clear
- post-exposure use of immune globulin or DAAs is ineffective in preventing HCV and is not recommended

6.13.3 PWID:

- strengthening and expansion of needle and syringe programmes and provision of opioid substitution therapy to reduce the spread of HCV, HBV and HIV in South Africa is required and noted in South Africa's *National Strategic Plan on HIV, TB and STIs* (2017 – 2021)
- treatment for this group should be prioritised as a means of avoiding further HCV transmission in an injecting group
- referral to organisations and individuals providing evidence-based substance use prevention, treatment and support services is recommended

6.13.4 Haemodialysis patients

Patients with renal failure on haemodialysis have a high risk of blood-borne viral infections:

- HCV seroprevalence ranges from less than 10 to 90 per cent in haemodialysis patients
- improved HCV NAT screening techniques will reduce the incidence of HCV infection
- nosocomial/HCAI transmission is the most probable cause of HCV in these patients when parenteral transmission cannot be identified
- strict adherence to universal precautions against nosocomial infections/HCAI reduces the risk of transmission [45]

6.14 Secondary Prevention

The following secondary prevention activities are recommended for HCV-infected persons:

- HCV testing should be offered to household and sexual contacts and injecting partners of PWID followed by counselling and linkage to treatment. This will enable proper medical management of the disease in infected persons as well as the introduction of control measures to prevent transmission to contacts
- those with chronic HCV should be advised to avoid alcohol and be given the appropriate support to achieve abstinence as alcohol exacerbates HCV liver disease
- HCV-infected patients should receive immunisation against HAV and HBV and be screened for HIV

6.15 Diagnostic, Prevention and Treatment Options at Primary, Secondary and Tertiary Levels of Care

6.15.1 Diagnosis:

- all levels of care: anti-HCV (EIA) and HCV PCR (NAT)
- secondary and tertiary level care: HCV RNA quantification
- tertiary level care: HCV genotype and HCV resistance associated substitution testing (RAS)

6.15.2 Assessment of clinical severity:

- all levels of care: FBC, INR, serum creatinine and liver profile; enables APRI scoring to assess for cirrhosis and choice of NUC
- secondary and tertiary levels of care: Ultrasound liver ± mobile fibroscan
- tertiary level care: Fibroscan and liver biopsy

6.15.3 Treatment:

- acute HCV:
  - diagnosing suspected acute HCV is clinically challenging and tertiary level referral is strongly advised
- chronic HCV
  - all HCV-infected individuals are candidates for DAA therapy
  - no DAAs are registered as yet in South Africa and presently all HCV-infected individuals are treated at tertiary level
  - a Section 21 SAHPRA application for DAA therapy must be made
- on registration of DAAs in South Africa:
  - uncomplicated cases of chronic HCV: Treat at secondary and tertiary levels of care or at community-based clinics for key populations (PWID and MSM)
  - cirrhotics (compensated and decompensated): Tertiary level care
  - HIV/HCV co-infection: Tertiary level care and with option of down-referral to secondary or primary level care, once HCV

- successfully treated and stable on ART
  - HBV/HCV/HIV co-infection: Tertiary level care and with option of down-referral to secondary or primary level care, once HCV
  - successfully treated and stable on ART

6.15.4 DAA regimens: 12 weeks therapy

- Sofosbuvir/Ledipasvir: Genotypes 1, 4, 5 and 6*
- Sofosbuvir /Daclatasvir: Genotypes 1 to 5*
- Sofosbuvir/Velpatasvir: Genotypes 1 to 6*
- Glecaprevir/Pibrentasvir: Genotypes 1 to 6

* If cirrhosis present, add Ribavirin or extend to 24 weeks of therapy

6.15.5 Prophylaxis:

- all levels of care:
- screening of contacts: anti-HCV
- HBV immunisation

HEPATITIS D (HDV)

CHAPTER 7

7.1 Introduction

HDV is a unique RNA virus that is dependent on HBV for survival. HDV is a defective or incomplete virus that does not encode its own replicase and is dependent on HBV providing HBsAg to coat its virion in order to replicate.[1,2] Thus, there are no viral replicative enzymes for drugs to target. Eight HDV genotypes have been identified and are associated with variable clinical courses. In Africa, where HBV is endemic, documented HDV seroprevalence rates vary geographically from low rates in countries south of the equator (0 to 0.6 per cent) to high rates north of the equator (two to67 per cent).[1,3] In South Africa, seroprevalence rates of 0 to 0.6 per cent are documented.[4-7] HDV co-infection should always be considered in stable HBV-infected individuals who deteriorate for no apparent cause if they originate from parts of Africa where HDV is more prevalent.

7.2 Transmission of HDV

HDV is transmitted via the parenteral route:

- sexual transmission
- perinatal transmission (MTCT): low risk
- IUD

7.3 Groups at Risk for HDV:

- individuals co-habitating with an HDV-infected HBsAg carrier in the setting of an overcrowded family household
- IUD: Risk of triple infection with HBV, HDV and HIV

7.4 Clinical Presentations of HDV:

- clinically, HDV-related disease can be separated into three entities.8 Refer to Chapter 5: HBV for signs and symptoms

7.4.1 Acute HBV/HDV co-infection (including fulminant hepatitis):

- if acquired in adulthood, more than 95 per cent of individuals will clear both HBV and HDV, although there is a greater risk of fulminant hepatitis than with acute HBV

7.4.2 Acute HDV super-infection of a patient with chronic HBV:

- can present as an acute hepatitis in a previously asymptomatic HBsAg carrier or result in further clinical deterioration in individuals with established HBV disease

7.4.3 Chronic HDV

- HBV replication is usually suppressed (low or undetectable HBV DNA) and HBeAg is negative

  HDV becomes chronic in 70 to 90 per cent of individuals with superinfection and there is more rapid progression to cirrhosis and decompensation, especially in PWID where end-stage liver disease can occur in less than two years
- increased risk of hepatocellular carcinoma
- HBV/HDV/HCV triple infection: HDV is usually the dominant virus, inhibiting the replication of HBV and HCV

7.5 Diagnosis of HDV:

- ccute HBV/HDV co-infection:
  - anti-HDV IgM-positive and detectable HDV RNA
  - HBsAg-positive and IgM anti-HBc-positive
- ccute HDV super-infection of patient with chronic HBV:
  - anti-HDV IgM-positive and detectable HDV RNA; HBsAg-positive
  - HBeAg and anti-HBe-positivity will depend on the phase of chronic HBV infection
- chronic HDV:
  - anti-HDV IgG-positive and detectable HDV RNA; HBsAg-positive
  - HBeAg and anti-HBe-positivity will depend on the phase of chronic HBV infection
- HBV DNA levels: Vary depending on the HBV replication
- markers of HDV infection decrease rapidly and disappear after the clearance of HBsAg
- diagnostic serology and HDV DNA not routinely available – refer to tertiary level care for diagnosis and management

7.6 Prevention of HDV:

- no immunoglobulin available
- no specific HDV vaccine
- HBV immunisation is effective prophylaxis against HDV

7.7 Treatment of HDV:

- current recommended treatment of compensated chronic HDV disease: Peginterferon-alfa given weekly for 48 weeks, leading to HDV RNA clearance in 17 to 47 per cent, but relapse is common.9 Low baseline HBsAg and HDV RNA titers may predict a positive response to therapy
- control of HDV infection may be associated with HBV reactivation requiring antiviral therapy
- liver transplantation for HBV/HDV cirrhosis has a better prognosis than transplantation for HBV cirrhosis

Refer all suspected cases to tertiary level care for diagnosis and management as new therapies are in development.[10]

HEPATITIS E (HEV)

CHAPTER 8

8.1 Introduction

Hepatitis E is caused by the hepatitis E virus (HEV), which is a major etiologic agent of enterically transmitted non-A, non-B, non-C viral hepatitis worldwide.[1-7] HEV is a small, single-stranded ribonucleic acid (RNA) virus. It has at least four different types: genotypes 1, 2, 3 and 4. 8,9 Genotypes 1 and 2 have been found only in humans.[8,9] Genotype 3 and 4 viruses circulate in several animals (including pigs, wild boars, deer) without causing any disease. There are clear differences in the epidemic potential of the various genotypes[1], 4 Documented seroprevalence rates in South Africa range between two and 29 per cent, suggesting that HEV is endemic in South Africa.[10-12] Both acute and chronic cases of HEV have been reported in South Africa.[13,14]

8.2 Transmission of HEV:15

- faecal-oral transmission:
  - ingestion of faecally contaminated food or water
  - person-to-person spread
- zoonotic transmission through consumption of raw/undercooked meat (pork or deer) of infected animals
- parenteral transmission has been described in:
  - blood transfusions[16]
  - perinatal transmission[17]

Compared to HAV, HEV is less resistant to environmental conditions such as temperature; and prolonged excretion of HEV in stool following symptomatic/asymptomatic infections is rare.The modes of transmission vary dependent on the HEV genotype.

8.2.1 Genotypes 1 and 2:

- epidemic outbreaks, usually faecal-oral transmission
- men are more likely to present with symptomatic disease, but most patients have a self-limiting hepatitis
- outbreaks of HEV have been documented in sub-Saharan Africa[7,18]

8.2.2 Genotypes 3 and 4:

- primarily a zoonosis associated with eating pork, deer and mussels
- parenteral transmission via blood transfusion and perinatal routes is described[16,17]

- usually asymptomatic or a mild disease
- increased risk for symptomatic disease in older men and HBV infected individuals

8.3 Groups at Risk for HEV

Individuals at higher risk for HEV infection include:

- people who are household/sexual contacts of infected individuals
- healthcare workers
- preschool children attending daycare centres, their parents and siblings
- employees of daycare centres
- residents and employees of closed institutions where personal hygiene is compromised
- individuals living in refugee camps or inter¬nally displaced persons camps
- handlers of domestic animals are at risk of occupational exposure
- individuals with chronic liver disease: These individuals are not at increased risk for infection, but are at risk for severe disease
- immunosuppressed individuals including solid organ transplants, HIV-positive individuals and individuals with haematological malignancies: These individuals are not at increased risk for infection, but are at risk for severe disease and potentially chronic infection
- food handlers: These individuals are not at higher risk for infection, but pose a higher risk of transmission

8.4 Clinical Presentations of HEV2

The clinical presentation is modulated by the underlying epidemiological pattern of a particular region, by genotype; and the immune status and age of the individual:

- mild fever during initial phase
- anorexia
- nausea and vomiting lasting for a few days
- abdominal pain
- pruritus, skin rash or joint pains
- jaundice
- slightly enlarged tender liver
- acute liver failure (rare cases)

8.4.1 The different levels of disease severity include:

a) mild subclinical illness:

- asymptomatic infections tend to be more common in children[19]

b) self-limiting acute hepatitis resembling HAV20

- attack rate highest in men aged 15 to 40 years (10 to 30 per cent)
- symptomatic acute hepatitis occurs in up to 15 per cent during an outbreak

c) severe disease

- pregnant women in the third trimester[21,22]
- individuals with chronic liver disease

d) chronic hepatitis: HEV RNA-positivity in stool or serum persisting for more than six months:

- solid organ transplant recipients, HIV patients and haematological malignancies[23-27]
- transaminitis is usually mild in the range of 100 to 300 U/L, usually not jaundiced
- progression to chronicity occurs in approximately 60 per cent immunosuppressed solid organ transplant recipients as a result of impaired specific T-cell responses
    - o rapid progression to cirrhosis can occur
    - o tacrolimus therapy is the main predictive factor for chronic hepatitis
- chronic hepatitis has only occurred with Genotype 3 infections[24]

8.5 Diagnosis of HEV

Elevated serum transminases (ALT and AST usually 10 to 100 times upper limit of normal) confirm the presence of an acute hepatitis:

- acute HEV: Positive anti-HEV IgM and positive HEV PCR (blood)
- previous exposure to HEV: Positive anti-HEV IgG
- chronic HEV: Positive anti-HEV IgG and a positive HEV PCR (blood) for more than six months

Most patients with acute HEV will also have anti-HEV IgG at initial presentation. Anti-HEV IgM levels decline rapidly during early convalescence, whilst anti-HEV IgG persists long term. HEV has been found to be the cause of deranged liver enzymes in a number of cases of hepatitis diagnosed as drug-induced liver injury. [28]

8.6 Treatment of HEV

8.6.1 Acute HEV:

- treatment of acute HEV is generally supportive
- refer patients with severe symptomatic disease and pregnant women to hospital
- liver transplantation: May be considered in patients presenting with fulminant liver failure
- adherence to standard infection and contact precautions is usually sufficient to prevent spread of infection in healthcare facilities and institutions
- sanitary disposal of faecal waste and strict hand hygiene is essential
- no special diet is required, but patients should be advised to abstain from alcohol and the use of any other hepatotoxic drugs
- exclusion from work and school for two weeks after the onset of jaundice, provided the AST and ALT levels are less than 100 U/L. Patients can only return to active sport or strenuous activity once AST and ALT levels have normalised
- adults should return to fulltime work before returning to sport

8.6.2 Chronic HEV:

- decrease in the immunosuppression: First step in management of chronic HEV in solid organ transplant recipients:
  - 30 per cent will clear HEV, if immunosuppression is reduced
- in the absence of an adequate response to reduced immunosuppression:
  - discuss the use of Ribavirin 600-800 mg/day for three months with a hepatologist
- overall mortality: 0.5 to four per cent
- increased mortality in certain groups:
  - children younger than three years: five to eight per cent[18, 20]
  - pregnant women in the third trimester: 25 per cent [21,22]
  - patients with chronic liver disease: 75 per cent[15]

8.7 Prevention of HEV

There is no iimmunoglobulin and the HEV vaccine is currently unavailable in South Africa.

8.7.1 General measures to prevent the spread of HEV:

- improving sanitation and safety of public water supplies
- maintaining good hygienic practices such as hand washing with soap
- standard food and water hygiene and infectious precautions are recommended:
- avoid intake of raw, uncooked meat to prevent zoonotic HEV transmission
- risk decreased by cooking the meat to temperatures higher than 70°C

8.7.2 Response to HEV outbreaks

All HEV outbreaks should prompt the following actions:

- notify the case investigate a single sporadic case, and an outbreak of HEV (≥2 epidemiologically linked cases) should be thoroughly responded to, by following the epidemic preparedness and response guidelines
- thorough environmental assessment including inspection of food preparation and common food sources, water quality and general hygiene
- if a common source outbreak is suspected and the source is unknown, further analytical epidemiology is required to determine the potential source

8.8 Diagnosis and Treatment Options: Primary, Secondary and Tertiary Levels of Care

8.8.1 Diagnosis:

- all levels of care: anti-HEV IgM and anti-HEV IgG
- tertiary level care: HEV PCR and HEV Genotype

8.8.2 Assessment of clinical severity:

- all levels of care: Liver profile and INR

8.8.3 Treatment:

- primary level care: Uncomplicated cases
- secondary level care: Symptomatic cases with jaundice, nausea and vomiting; but no encephalopathy and INR<2: Intravenous fluids and monitoring of synthetic function
- tertiary level care:
    - acute liver failure (jaundice, encephalopathy and INR>1.5): Preferably with potential access to liver transplantation
    - chronic HEV

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CHAPTER 9

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SUMMARIES AND TREATMENT ALGORITHMS FOR HBV AND HCV

APPENDIX

1. Summary of Main Characteristics of HBV

HBV is endemic in South Africa, resulting in a significant burden of clinical disease. Patients with chronic HBV infection have a 15 to 40 per cent risk of developing cirrhosis, liver failure or hepatocellular carcinoma (HCC)/liver cancer, and 15 to 25 per cent risk of dying from HBV-related liver diseases.

The risk of chronic infection is dependent on the age of first infection: 70 to 90 per cent for infants exposed perinatally (from an HBeAg-positive mother); 25 to 50 per cent for children between one and five years; six to 10 per cent for five to 20 years and one to three per cent for adults older than 20 years.

HBV is an entirely vaccine-preventable disease.

EPIDEMIOLOGY AND TRANSMISSION IN SOUTH AFRICA:

- estimated 6.7 per cent HBsAg seroprevalence in low risk groups. Up to 25 per cent in HIV infected individuals
- parenteral transmission: Main route of transmission is horizontal between ages six months to five years. Other routes of parenteral transmission include perinatal, sexual and percutaneous routes
- increased risk of perinatal transmission in HIV/HBV coinfected mothers

CLINICAL PRESENTATIONS:

- acute infection: Usually asymptomatic and subclinical in neonates and children. Adolescents and adults usually present with symptomatic hepatitis with/without jaundice
- fulminant hepatitis with acute liver failure (0.1 to 0.5 per cent)
- Chronic infection - five different phases of infection.

  Depending on the phase of infection, the individual maybe completely asymptomatic or present with a hepatitis flare or complications of cirrhosis including jaundice, portal hypertension (varices and ascites) and hepatocellular carcinoma. Hepatocellular carcinoma can occur in the absence of cirrhosis
- extrahepatic manifestations

Can occur in both acute and chronic HBV:

- polyarteritis nodosa
- membranous glomerulonephritis
- membranoproliferative glomerulonephritis

DIAGNOSIS:

- depends on combination of ALT, HBV serology, HBV DNA levels and non-invasive markers of fibrosis.
- liver biopsy seldom required

Intepretation of serological markers, HBV DNA and ALT levels	
Successful immunisation	• positive anti-HBsAb (titre >10 IU/ml)
Previous exposure to HBV	• positive HB IgG core antibody +/- positive anti-HBsAb
Acute HBV	• HBsAg positive, HB IgM core antibody positive • elevated ALT
Fulminant hepatitis	• may be HBsAg-negative, but HB IgM core antibody positive • HBV DNA detectable • elevated ALT • Synthetic dysfunction (elevated ammonia and prolonged INR>1.5)
Chronic HBV ALT, serology and HBV DNA levels depend on phase of chronic infection	
HBeAg-positive chronic HBV infection (immune tolerant)	• HBsAg-positive, HBeAg-positive • hhigh HBV DNA (usually >200 000 IU/ml, typically >1M IU/ml) • normal ALT
HBeAg-positive chronic hepatitis (immune clearance)	• HBsAg-positive, HBeAg-positive • HBV DNA >20 000 IU/ml • elevated ALT
HB-eAg-negative chronic HBV infection (immune control)	• HBsAg-positive, HBeAg-negative • HBV DNA <2 000 IU/ml • normal ALT
Chronic HBV ALT, serology and HBV DNA levels depend on phase of chronic infection	
HB-eAg-negative chronic hepatitis (immune escape)	• HBsAg-positive, HBeAg-negative • HBV IgM core antibody maybe low positive with a flare • HBV DNA >2 000 IU/ml • fluctuating elevated ALT
Occult HBV infection	• HBsAg-negative, anti-HBsAb-negative, • HBV IgG core antibody positive • HBV DNA <200 IU/ ml • normal ALT

ASSESSMENT OF LIVER DISEASE AND NEED FOR THERAPY:

- establish phase of chronic infection
- detailed clinical history and physical examination
- assessment of the severity of the liver disease:
  - liver profile: total bilirubin, conjugated bilirubin, ALT, AST, ALP, GGT
  - FBC including a differential count
  - Albumin and INR to assess synthetic function
- look for other co-factors
  - viral co-infection: HIV, HCV
  - alcohol
  - non-alcoholic fatty liver disease
  - iron overload
  - drug/toxin-induced liver injury
- serological assessment
  - HBsAg, anti-HBs, HBeAg and anti-HBe ± HB IgM Ab (note – can be low positive with a flare)
  - hhepatitis B IgG core antibody (if assessing for occult HBV or previous cleared infection)
  - anti-HAV IgG to assess need for HAV immunisation
- Alpha fetoprotein
- ultrasound of the liver and dopplers
- non-invasive markers of fibrosis:

- APRI score = (AST/ULN) x 100) / platelet count (109/L)

  APRI score >2 identifies adults with cirrhosis (F4) and in need of antiviral therapy
- vibration controlled transient elastography (FibroScanR)

- liver biopsy no longer routinely required
  - excluding other contributing forms of acute/ chronic liver disease e.g. Drug or toxin-induced liver injury

GOALS OF THERAPY:

- prevention of long-term complications of chronic HBV
  - cirrhosis
  - liver failure
  - hepatocellular carcinoma
- prevention of reactivation in setting of immunosuppression/biologicals/chemotherapy
- ensure HBV viral suppression in ALF

Ideal endpoint of treatment: Immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to anti-HBs. Virological cure not yet possible.

INDICATIONS FOR TREATMENT:

Patients requiring treatment	Monitoring required
• acute liver failure• compensated or decompensated cirrhosis (APRI score >2 in adults) o regardless of ALT levels, HBeAg status or HBV DNA levels • patients receiving chemotherapy, rituximab or immunosuppressive therapy • HBeAg-positive chronic HBV (immune clearance) • HBeAg-negative chronic HBV (immune escape)	• HB-eAg-negative chronic HBV infection (immune control) • HB-eAg-positive chronic HBV infection (immune tolerance)

TREATMENT OPTIONS:

- NUCs: TDF, TAF, Entecavir and Lamivudine
- interferon-based therapy: Pegylated Interferon – only under the supervision of a hepatologist

Tenofovir is the preferred NUC. TAF and Entecavir is reserved for patients with renal impairment. Lamivudine should not routinely be used because of high rate of resistance.

TREATMENT OF SPECIAL POPULATIONS:

- pregnancy: (see PMTCT)
  - HBsAg screening of pregnant women is essential
  - indications for therapy: same as usual indications
- HBV/HCV co-infection:
  - treat HBV before treating HCV
- HIV/HBV co-infection:
  - All should be treated with an ARV regimen that includes Tenofovir and lamivudine or emtricitabine
- healthcare workers:
  - HBV DNA level should preferably be undetectable or <200 IU/ml before practicing exposure-prone procedures

PREVENTION:

HBV immunisation:

- recommend HBV birth dose as part of EPI to prevent perinatal transmission
- ideally all South Africans should be vaccinated
- high-risk groups must be vaccinated:
  - healthcare workers
  - all laboratory workers working with clinical specimens
  - police, firefighters and members of the armed forces
  - persons with end stage renal disease requiring dialysis
  - persons who inject or use drugs
  - household contacts of HBsAg-positive persons

- sex partners of HBsAg-positive persons
- residents and workers of facilities for the developmentally disabled
- patients receiving frequent transfusions of blood or blood components
- transplant candidates before transplantation
- persons seeking evaluation for treatment of a sexually transmitted disease
- MSM
- persons with chronic liver disease
- persons with HIV infection
- workers and residents of correctional service facilities

Post-exposure prophylaxis: Needle stick/ sexual exposure/percutaneous exposure:

- wounds washed with soap and water
- mucous membranes flushed with water
- source individual screened: HBsAg, HIV and anti-HCV
- exposed individual screened: HBsAg, HBsAb and HB IgG core Ab:
  - infected, immune or non-immune
- source individual HBsAg-positive or status unknown and exposed individual non-immune:

o HBIG (0.06ml/kg or 500IU) IMI and active immunisation (0.1 and two months)

- consider repeat HBIG at one month:
  - if contact HBeAg-positive or high DNA levels
  - if exposed individual known non-responder

Prevention of MTCT:

- pregnant women: Tenofovir if HBV DNA > 200 000 IU/ml, starting at 28 to 32 weeks gestation
- neonate: HBV birth dose vaccine and HBIG at different sites within 12 to 24 hours of delivery

  Complete EPI HBV vaccine schedule at six,10 and 14 weeks

Diagnostic, prevention and treatment options at primary, secondary and tertiary levels of care:

DIAGNOSIS:

- viral serology (HBsAg, anti-HBs, HBeAg, anti-HBe, IgG and IgM anti-HB core at all levels of care)
- HBV DNA quantification at secondary and tertiary levels of care

Assessment of clinical severity:

- liver profile and INR at all levels of care; enables APRI scoring to assess for cirrhosis
- ultrasound liver : Secondary and tertiary levels of care
- fibroscan and liver biopsy: Tertiary levels of care

TREATMENT:

- acute HBV:
  - uncomplicated cases managed at primary care level including screening at

    six months to exclude progression to chronic HBV
  - complicated cases with synthetic dysfunction: Refer to secondary care level
  - fulminant hepatitis: Refer to tertiary care level
- Chronic HBV:
  - HB-eAg-negative chronic HBV infection (immune control): Follow up at primary care level
  - HB-eAg-positive chronic HBV infection (immune tolerant): Follow up at primary care level
  - HBeAg-positive chronic hepatitis (immune clearance): Tertiary level care with option of down-referral

    to secondary or primary level care when stable on therapy
  - HBeAg-negative chronic hepatitis (immune escape): Tertiary level care with option of down-referral

    to secondary or primary level care when stable on therapy

- cirrhotics (compensated and decompensated): Tertiary level care
- HIV/HBV, HBV/HCV and HBV/HCV/HIV: Tertiary level care with option of down-referral to

  secondary or primary level care when stable on therapy

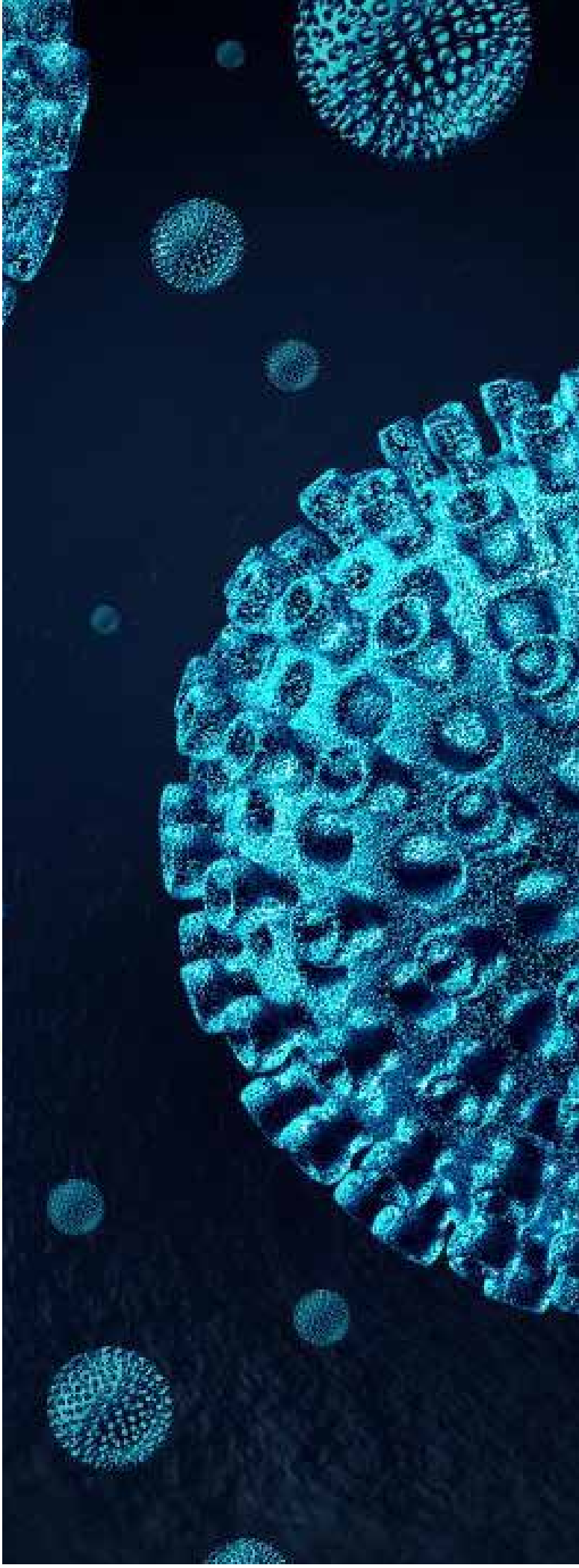
Therapeutic options:

- Lamivudine and TDF : at all levels of care for both HBV mono-infected and HBV/HIV co-infected
- Entecavir,TAF and Pegylated Interferon at tertiary care level

Prophylaxis:

- HBV immunisation: all levels of care
- HBIG: all levels of care

ENTER YOUR PATIENT CHARACTERISTICS FOR INSTANT GUIDANCE ON MANAGEMENT CLINICALOPTIONS.COM/ HEPBCONSULT



Guidance: Monitor vs Treat in HBeAg-Positive Patients

Noncirrhotic HBeAg-Positive Patients

ALT ≤ ULN*

HBV DNA > 20,000 IU/mL
- **Monitor** ALT, HBV DNA every 3-6 mos x 1yr
  - then 6 monthly
- **Monitor** HBeAg annually

***Upper limit of normal (ULN) for ALT in healthy adults:**
- 29-33 U/L for men
- 19-25 U/L for women
- **The ULN of 35 U/L for men and 25 U/L for women is recommended to guide treatment**

First-line therapy
- **NUC: TDF or Entecavir or TAF**
- **Peylated Interferon**

ALT ≥ ULN but ≤ 2 x ULN*

HBV DNA > 20,000 IU/mL†
- **Exclude other causes of ALT elevation**
  - **Treat if ALT elevation persists, especially if > 30 yrs of age**
- **Evaluate fibrosis/Inflammation**
  - **Treat if ≥ F2 or ≥ A3**

ALT ≥ 2 x ULN*

HBV DNA > 20,000 IU/mL
- **Treat**

HBV DNA 2000-20,000 IU/mL†
- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists,**
  - **especially if > 30 yrs of age**
- Evaluate fibrosis/Inflammation
  - **Treat if ≥ F2 or ≥ A3**

†Additional note if HBV DNA 2000-20,000 IU/mL (which may represent seroconversion)
- **Monitor** DNA every 1-3 mos
  - **Treat if HBV DNA > 2000 IU/mL persists for > 6 mos**

Guidance: Monitor vs Treat in HBeAg-Negative Patients

Noncirrhotic HBeAg-Negative Patients

ALT ≤ ULN*

HBV DNA > 2000 IU/mL
- **Monitor** ALT, HBV DNA every 3 mos for 1 yr, then every 6 months
- **If unable to monitor closely-Treat**

HBV DNA <2000 IU/mL (Immune control)
- **Monitor** ALT, HBV DNA every 3 mos for 1 yr, then every 6-12 months
- **Monitor** HBsAg annually

ALT ≥ ULN but ≤ 2 x ULN*

Any Detectable HBV DNA
- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists, especially if > 30 yrs of age**
- Evaluate fibrosis\inflammation
  - **Treat if ≥ F2 or ≥ A3**

ALT ≥ 2 x ULN*

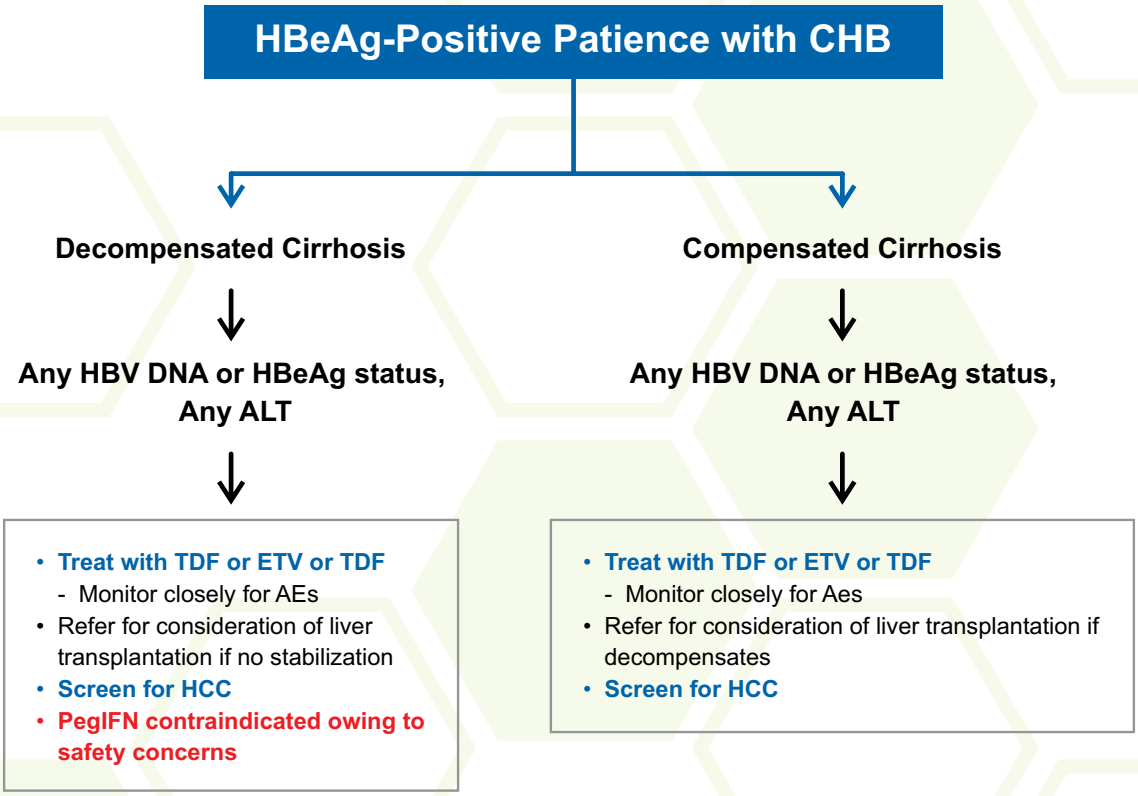
HBV DNA > 20,000 IU/mL
- Treat

HBV DNA < 2000 IU/mL †
- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists, especially if > 30 yrs of age**
- Evaluate fibrosis\inflammation
  - **Treat if ≥ F2 or ≥ A3**

***The upper limit of normal (ULN) for ALT in healthy adults:**
- 29-33U/L for men
- 19-25U/L for women
- **The ULN of 35 U/L for men and 25 U/L for women is recommended to guide treatment**

First-line therapy
- NUV: TDF or Entecavir or TAF
- Pegylated Interferon

Guidance: Cirrhosis



2. Summary of Main Characteristics of HCV

The true burden of chronic HCV in South Africa is not clear, however a high prevalence in at risk groups exist. Following primary infection, 15 to 45 per cent of infected persons spontaneously clear HCV within six months with 55 to 85 per cent developing chronic HCV infection. Genotypes 1 to 5 are found in South Africa with genotype 5a being unique to South Africa.

EPIDEMIOLOGY AND TRANSMISSION IN SOUTH AFRICA:

- HCV seroprevalence and transmission is incompletely characterised
- available data suggests 0.01 to 2.6 per cent seroprevalence in urban blood donors (low risk)
- new data suggests high prevalence in PWID
- parenteral transmission
- sexual transmission is infrequent except in high risk behaviour and MSM
- vertical transmission requires high viral titres as found HIV/HCV co-infected individuals
- high-risk groups include:
  - recipients of blood, blood products and organs pre-1992
  - PWID
  - use of intranasal cocaine
  - occupational exposure e.g. HCWs with needle stick injuries
  - haemodialysis patients
  - tattoos, body piercing, acupuncturing with unsafe equipment
  - infants born to HCV-positive mothers
  - high-risk sexual practices
  - surgical procedures including dental/ orthodontic procedures before efficient sterilisation procedures were in place

CLINICAL PRESENTATIONS:

- acute infection: 80 to 90 per cent are asymptomatic. Seldom diagnosed as usually subclinical
- fulminant hepatitis: Extremely rare
- chronic infection: Usually asymptomatic until presentation with complications of cirrhosis.

20 per cent may have persistently normal ALT that does not correlate with lack of disease progression

- HCV/HIV co-infection: Accelerated risk of cirrhosis
- extrahepatic manifestations:
  - autoimmune (e.g. Sjögren's syndrome, Cryoglobulinaemia, Sialadenitis, Polyarteritis nodosa)
  - porphyria cutanea tarda
  - lymphoproliferative diseases e.g. B-cell non-Hodgkin's lymphoma)
  - progressive insulin resistance, impaired fasting glucose and/or frank type 2 diabetes mellitus

DIAGNOSIS:

- anti-HCV (EIA): 95 per cent sensitivity. Detecting antibody in 80 per cent within five to six weeks of infection
- qualitative PCR: Confirmatory nucleic acid testing (NAT) detects HCV within one to three weeks of infection
- quantitative PCR: Assesses viral load and treatment response
- genotype testing: To determine appropriate therapy regimen (not necessarily required with pangenotypic therapy)

TREATMENT AND PREVENTION:

No vaccine or passive immunoglobulin available.

Virological cure is attainable and is sustainable in more than 99 per cent of individuals irrespective of the type of treatment.

DIRECT ANTIVIRAL AGENTS:

There are no DAAs currently registered by SAHPRA in South Africa. They are obtainable via a Section 21 certification process. SVR rates for DAA therapies exceed 90 per cent for 12 weeks treatment in non-cirrhotics.

Previous treatment, viral load, IL28B, presence of cirrhosis are no longer negative factors influencing SVR. Treatment duration and need for Ribavirin is influenced by cirrhosis. Need for monitoring is limited and side-effects are minimal. DAA therapy is effective in the HIV/HCV co-infected, liver transplant patients and those with chronic kidney disease.

All patients with chronic HCV are eligible for treatment. Pre-treatment check for drug-drug interactions with patients existing drug treatments is mandatory: www.hep-druginteractions.org or HEP iChart (Android or Apple)

DAA regimens in treatment naive patients:

- Sofosbuvir/Ledipasvir : Genotypes 1, 4, 5 and 6*
- Sofosbuvir /Daclatasvir: Genotypes 1 to 5*
- Sofosbuvir/Velpatasvir: Genotypes 1 to 6*
- Glecaprevir/Pibrentasvir: Genotypes 1 to 6

  * If cirrhosis present, add Ribavirin or extend to 24 weeks of therapy

  If patient DAA experienced, consult an expert

  With pangenotypic regimen, genotyping can be omitted

DIAGNOSTIC, PREVENTION AND TREATMENT OPTIONS AT PRIMARY, SECONDARY AND TERTIARY LEVELS OF CARE:

Diagnosis:

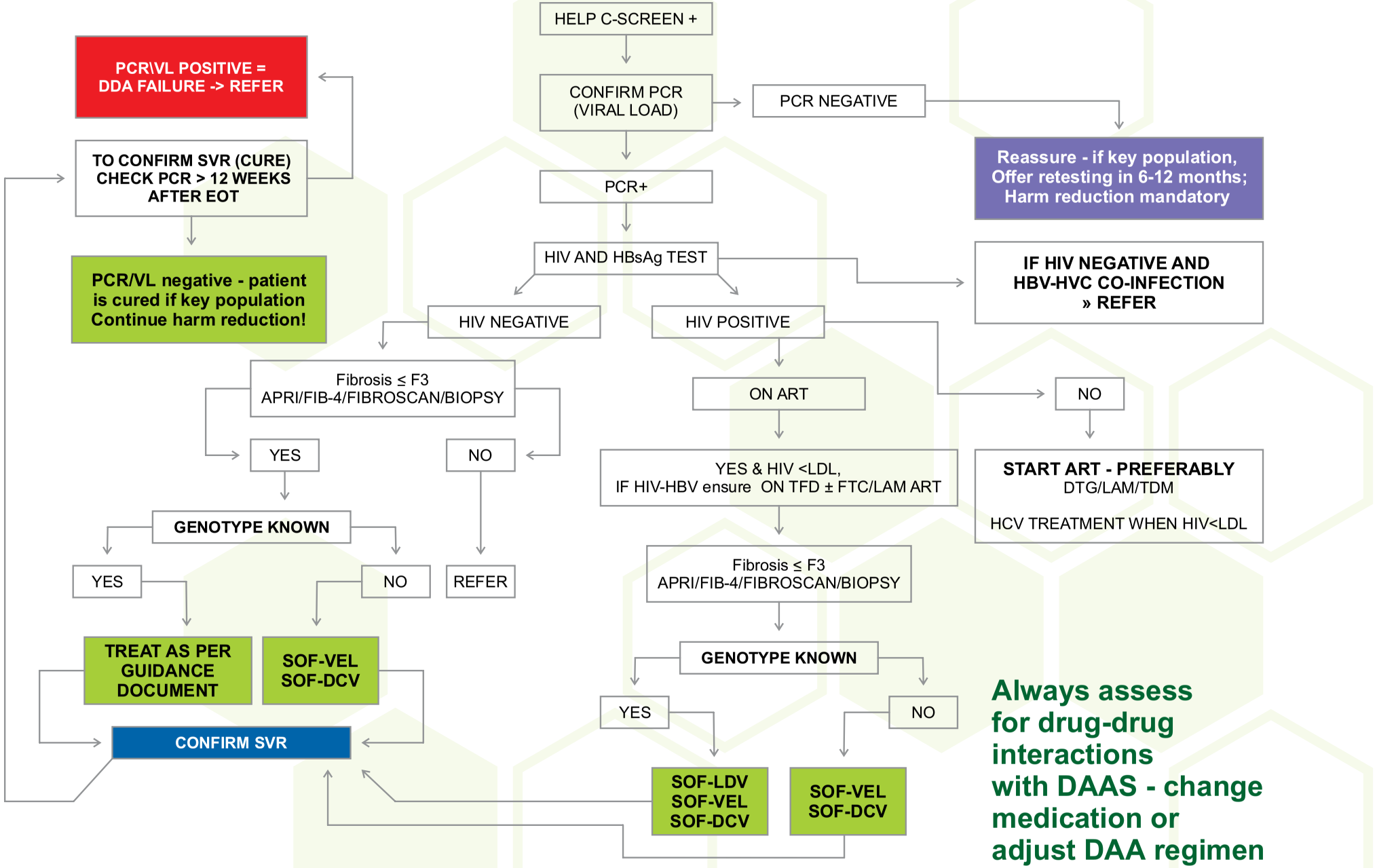
- anti-HCV (EIA): All levels of care
- HCV PCR (NAT): All levels of care
- quantitative HCV PCR, Genotype and RAS testing: Tertiary care level

Assessment of clinical severity:

- liver profile and INR at all levels of care; enables APRI scoring to assess for cirrhosis
- ultrasound liver: Secondary and tertiary care levels
- liver biopsy and FibroScanR: Tertiary care levels

Treatment:

Currently refer to tertiary care level and apply for Section 21 SAHPRA permission for DAA therapy.

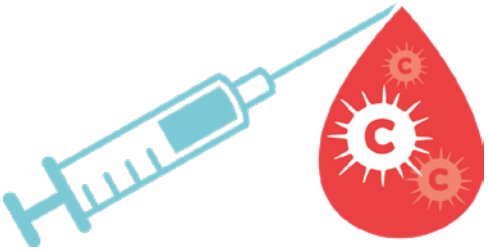

HELP C-SCREEN +
CONFIRM PCR (VIRAL LOAD)
PCR NEGATIVE
Reassure - if key population, Offer retesting in 6-12 months; Harm reduction mandatory
PCR+
HIV AND HBsAg TEST
IF HIV NEGATIVE AND HBV-HVC CO-INFECTION » REFER
HIV NEGATIVE
HIV POSITIVE
Fibrosis ≤ F3 APRI/FIB-4/FIBROSCAN/BIOPSY
YES
NO
GENOTYPE KNOWN
YES
NO
REFER
TREAT AS PER GUIDANCE DOCUMENT
SOF-VEL SOF-DCV
CONFIRM SVR
PCR\VL POSITIVE = DDA FAILURE -> REFER
TO CONFIRM SVR (CURE) CHECK PCR > 12 WEEKS AFTER EOT
PCR/VL negative - patient is cured if key population Continue harm reduction!
ON ART
NO
START ART - PREFERABLY DTG/LAM/TDM
HCV TREATMENT WHEN HIV<LDL
YES & HIV <LDL, IF HIV-HBV ensure ON TFD ± FTC/LAM ART
Fibrosis ≤ F3 APRI/FIB-4/FIBROSCAN/BIOPSY
GENOTYPE KNOWN
YES
NO
SOF-LDV SOF-VEL SOF-DCV
SOF-VEL SOF-DCV
Always assess for drug-drug interactions with DAAS - change medication or adjust DAA regimen

NOTES:

Introduction to hepatitis C

The word *hepatitis* comes from the Ancient Greek word for liver (*hepar*) and the Latin word for inflammation (*itis*). Chemicals, drugs, excessive alcohol consumption or blood-borne viruses can all cause inflammation to the liver.

What is hepatitis C?



Hepatitis C is an infection caused by the hepatitis C virus that causes inflammation of the liver. Infection can occur through blood-to-blood contact due to unsafe injection and other skin penetration practices, inadequate sterilisation of medical equipment, and the transfusion of unscreened blood and blood products.

Currently, there is no vaccine for hepatitis C virus, as there is for hepatitis A and hepatitis B. A person can be re-infected throughout their life and can live with more than one hepatitis virus at once.

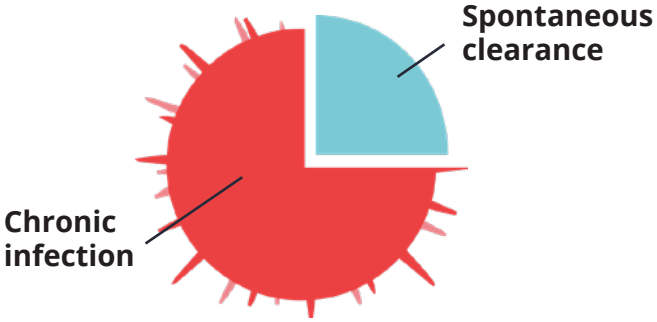
Symptoms and diagnosis

HCV infection can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness.

Common symptoms of acute infection are:

- General aches and pains
- Nausea
- Abdominal pain and discomfort
- Loss of appetite
- Rarely yellowing of the eyes and skin (jaundice)

About 25% of people infected will clear the virus naturally in the first 12 months (**acute infection**).



However, if the infection does not clear up on its own, the virus continues to damage the liver. Of those who are exposed to hepatitis C, up to 75% will go on to develop **chronic infection**.

A person living with chronic hepatitis C may not know they have it because it can take many years for symptoms to appear. Consequently, many people live undiagnosed for years. Some cannot identify how they were infected.

Impact on the liver

Over time Hepatitis C infection can seriously impair liver function, causing fibrosis or cirrhosis (scarring of the liver), and can lead to hepatocellular carcinoma (HCC).

The rate of progression to cirrhosis is variable and depends on several factors, including age of initial infection, male gender, alcohol consumption, co-infections including HIV and hepatitis B virus, and obesity. Around 10-15% of people living with chronic HCV infection will develop cirrhosis within the first 20 years after infection; those who develop cirrhosis are at increased risk of HCC.

Geographical distribution

Globally, there about 70 million people living with hepatitis C, a figure which represents roughly 1% of the population[1] . The regions most affected are Africa and Central and East Asia.

1%

70 million people

Hepatitis C genotypes

There are six main genotypes (viral strains) of HCV worldwide, each with numerous subtypes, and their distribution varies by region. Knowing the genotype is important when making decisions about treatment.

New treatments

Unlike HIV and HBV infection, hepatitis C infection can be cured.

Testing for the virus is simple and the new generation treatments are far more effective, easier to take and have fewer side-effects than the older medications.

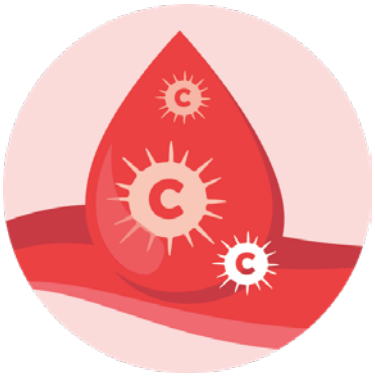
[1] The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterology and Hepatology 2016 Dec 15. http://dx.doi.org/10.1016/S2468-1253(16)30181-9

How hepatitis C spreads

The hepatitis C virus is a blood-borne virus, meaning it's transmitted when the blood of an infected person enters another person's bloodstream. It only takes a small amount of blood to transmit hepatitis C. The virus can live outside of the body for at least four days. In other conditions, it can survive for much longer (e.g. for many weeks inside a syringe).

Understanding the risks

There are many myths about exactly how hepatitis C is transmitted. It is important to know that the riskiest activities are those with the highest potential and frequency of blood-to-blood contact. Those activities that have no chance of exchanging blood are considered no risk. Based on these distinctions, high-risk, some-risk and no-risk activities are outlined below.



High-risk activities

- Unsterile medical or dental procedures and traditional medical practices where the skin is pierced.
- Re-using someone else's injecting equipment for drugs.
- Unsterile tattooing or body piercing.

Moderate-risk activities

- Needle-stick injuries to healthcare workers.
- Mother-to-child transmission may happen during pregnancy or childbirth if mother has hepatitis C.
- Received blood transfusion before September 1991 in the UK.
- Re-using someone else's personal items that may have blood on them, such as razors and toothbrushes.
- Blood-to-blood contact during sex.

No-risk activities

If there is no blood-to-blood contact, there is no risk of transmission of hepatitis C. People cannot get or transmit hepatitis C by:

- Sharing toilets, drinking glasses or eating utensils
- Hugging, kissing or touching
- Using swimming pools
- Mosquito or other insect bites
- Coughing or sneezing

Risks for people living with hepatitis C

Understanding how hepatitis C is transmitted is important for people who are living with hepatitis C so they can reduce the chance of:

Being infected with another genotype of hepatitis C.

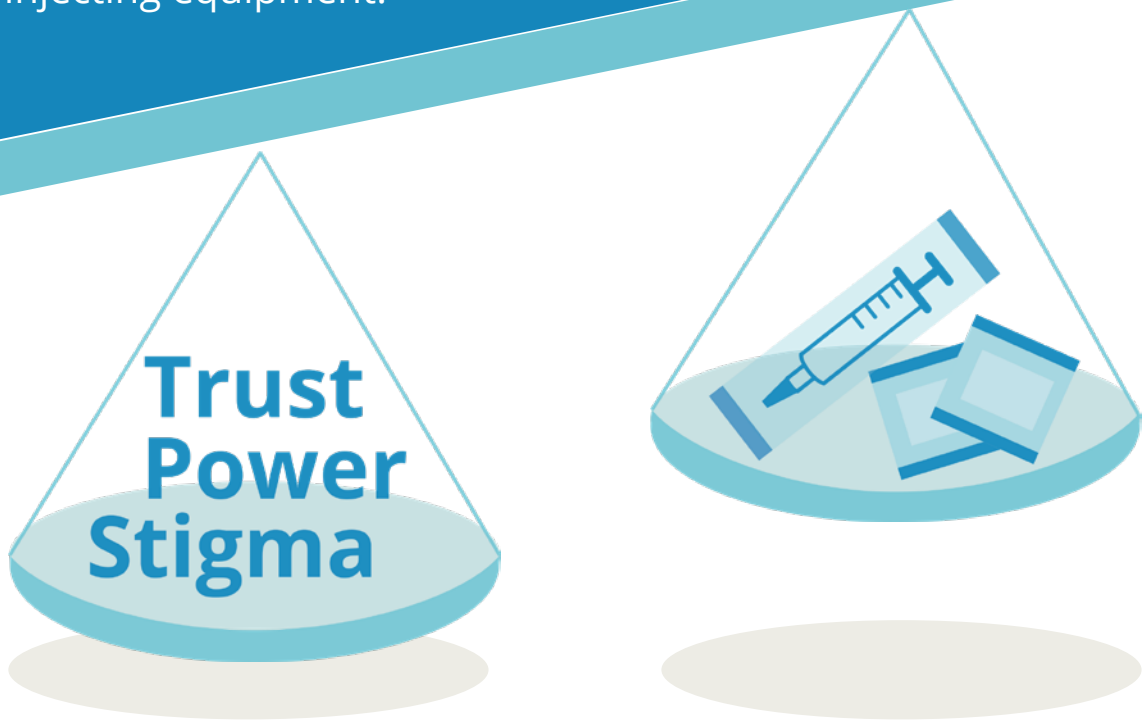
Being re-infected with the same genotype of hepatitis C.

Transmitting hepatitis C to another person.

INHSU

Something to think about: **injecting in the real world**

There are multiple reasons why someone who injects drugs may not feel able to access new, sterile injecting equipment.



Sometimes people who inject drugs may be part of social networks where they are unable to exercise full control over the circumstances in which they inject. For example, in some intimate or familial relationships, voicing an expectation that each person will use their own sterile equipment may be interpreted as implying a lack of trust, making a person uncomfortable or unwilling to jeopardise their relationships in this way.

In other situations, there may be a power imbalance between people who inject together which prevents the person with less power in the relationship from demanding that each person use their own, new equipment. This might be the case, for example, in a relationship between an older man with years of injecting experience and a younger woman who has injected for only a year or two and relies on her partner to purchase and prepare the drugs.

Some people may never have learnt to inject themselves, and rely on others to do it for them. In this case, they are dependent on the person injecting them to be willing to prepare the injections using new equipment, and the experienced injector may be unable or unwilling to do so. In prison, the extremely limited access to injecting equipment means that people who inject drugs in this environment inevitably do so with used equipment.

It is helpful if you acknowledge patients' best intentions while recognising the reality of their lived constraints.

For example, Needle and Syringe Programmes may have uneven distribution. This, combined with stigma and discrimination that some drug users may experience when accessing equipment, and the potential that their confidentiality may be breached and they will be identified as someone who injects drugs, can leave people reluctant to use services.

People may also be reluctant to access NSPs if they feel their eligibility for OST may be threatened, for example if their access points for both OST and sterile equipment are co-located.

If, however, your patient is able to and comfortable accessing their local Needle and Syringe Programme, you could advise them to, where possible, stock up with more injecting equipment than they think they might need ("so there's always some spares, for you or anyone else who might need them"). Patients may also find it useful to make contact with their local peer organisation to access advice and support from people who understand and can relate to their circumstances.

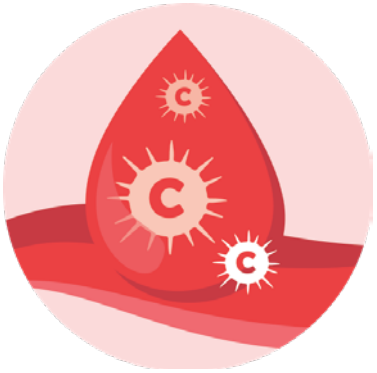
Hepatitis C virus testing and baselining

Has the person ever been exposed to HCV?

Test 1 - The Antibody (Ab) test

A positive HCV Ab result indicates that the person has been exposed to the virus at some point in their life. Note that:

- A positive HCV Ab test result does not distinguish between acute, chronic or cleared infection.
- The presence of HCV antibodies does not provide protection against HCV.



A negative result means that current HCV infection is unlikely. The HCV antibody test has low rates of false negatives or positives. However, this test may need to be repeated if the person has been exposed to risk recently (and possibly tested during the 'window period').

A small number (<5-10%) of immunocompromised hosts, including people living with HIV, may never develop HCV Ab, despite chronic HCV infection. In this case, HCV RNA testing should be performed to diagnose active HCV infection.

Does the person currently have HCV?

Test 2 - The RNA test

This can be determined by ordering a HCV RNA test. This is a test to detect the presence of virus in the blood, by Polymerase Chain Reaction (PCR). The HCV RNA test may be qualitative or quantitative. A positive result confirms the detection of HCV RNA and current viraemic HCV infection.

Ab
Antibody test EVER come into contact with HCV

RNA
Infected with the virus NOW

Ab + + RNA + = **Infected** with HCV **NOW**

Ab + + RNA – = **Infected** with HCV in the **PAST**

Ab – + RNA – = **NEVER** infected with HCV

What HCV genotype do they carry?

AA HCV genotype test is necessary for treatment options that are genotype-specific. HCV genotyping is a routine laboratory test performed during RNA testing.

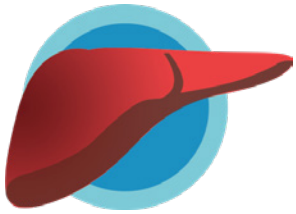
Pan genotypic treatment regimens are also available making all genotypes easier to treat.

Check your local guidelines for what treatment options are available.

What is the HCV RNA level (HCV “viral load”)?

Quantitative HCV RNA at treatment commencement (baseline) may help predict a person’s response to therapy. A low pre-treatment HCV RNA (“viral load”) may allow for a shorter duration of therapy. The length of therapy should be discussed with your local support network who can advise on the most appropriate regimen and its duration.

How is their liver functioning?



Liver Function tests (LFTs) provide a baseline of current liver function and help identify damage to liver cells. The relevant component tests of a routine LFT are bilirubin, ALP, GGT, ALT and AST. Documentation of the presence or absence of cirrhosis influences treatment regimen and duration.

Consent and confidentiality

In your discussions with your patient, you need to ensure they are well informed of the testing process, and you should obtain their verbal informed consent to proceed with testing. You have an opportunity to educate your patient on how to prevent HCV transmission, and assure them of your confidentiality through the discussion.

Gaining informed consent

- Inform the patient of your confidentiality and alleviate any anxiety they have regarding this
- Enquire about their motivation for getting tested
- Provide clear, appropriate information about HCV, including natural history and modes of transmission
- Explain the process of testing, window period and possibility of indeterminate results
- Discuss benefits of early detection
- Assess their ability to cope with positive result and social supports
- Supply written material about HCV (excellent resources for patients are available from www.hepctrust.org.uk)

Conveying test results

- Always give test results in person where possible
- Explain the meaning of the result and discuss immediate implications for the patient
- Avoid overloading the person with information
- Provide emotional support
- Reinforce education about transmission prevention and harm reduction
- Allow adequate time to answer the patient's questions
- Advise on aspects of positive status disclosure
- Arrange any further tests and offer follow-up as required
- Supply written material and contact details for relevant support services and/or peer-based drug users' organisation.

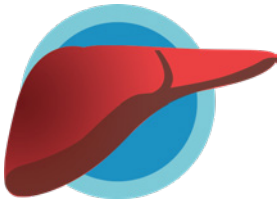
How to test for fibrosis

Once HCV has been diagnosed, the degree of liver fibrosis needs to be determined, as accurate staging will determine appropriate treatment and monitoring.

Non-invasive assessment

Although fibrosis assessment is imperative, liver biopsy is no longer required for most patients with chronic HCV infection. Non-invasive assessment of fibrosis has eliminated the need for biopsy in the majority of patients, and histologic confirmation of clinically evident cirrhosis is not required.

Liver ultrasound



Liver imaging may be used to assess for complications of cirrhosis, including hepatocellular carcinoma and portal hypertension. An ultrasound is preferred over CT scan as the initial investigation to avoid unnecessary radiation.

- If the ultrasound shows an abnormality, such as a nodule, more accurate cross-sectional imaging, such as computed tomography scan or magnetic resonance imaging scan, with and without contrast, would be indicated.

FibroScan®

FibroScan® is most accurate in identifying patients:

- Without significant fibrosis (<7.5 kPa)
- With cirrhosis (>11.5 kPa)

It is important to note that:

- Diagnostic accuracy declines when attempting to determine intermediate stages of fibrosis.
- Liver stiffness is increased independently of the degree of fibrosis in inflammatory liver conditions (E.g. acute HCV infection, acute alcoholic hepatitis or non-alcoholic steatohepatitis).
- Hepatic steatosis may increase the liver stiffness measurement obtained by FibroScan®. Abdominal obesity may overestimate the FibroScan® score – make sure the appropriate sized probe is used for each patient.
- FibroScan® does not give a reason for fibrosis or provide info on other liver pathology.

How FibroScan® works

An ultrasonic transducer sends a vibration wave into the liver. The velocity of the wave correlates with tissue stiffness. The stiffer the liver is, the greater the degree of fibrosis.

FibroScan® examination

Ideally, a patient should have fasted for 4 hours before the procedure.

While the patient is lying down, the probe is placed on the skin over the liver area, typically in the right mid-axillary line. Generally 10 measurements are taken to exclude outliers. The patient feels a gentle 'flick' each time a vibration wave is generated by the probe.

The whole procedure takes 5-10 minutes to perform, causes no discomfort, and results are available immediately.

APRI score

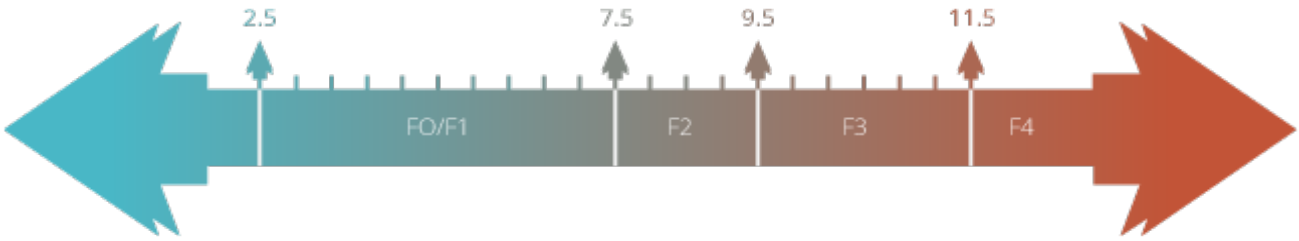
Although serum biomarkers have a role in patient management, they should not be over-interpreted.

In general, FIB-4 or APRI is most accurate for identifying patients at both ends of the spectrum of hepatic fibrosis: those at low risk for early or minimal disease (fibrosis stage 0 to 1) and those at high risk for advanced disease (fibrosis stage 3 to 4).

FibroScan® staging – understanding a FibroScan® result

The FibroScan® provides a numerical score of liver stiffness, which indicates the severity of liver fibrosis.

The diagram below show what FibroScan® scores mean.



Score	2.5 – 7.4	7.5 – 9.4	9.5 – 11.4	> 11.5
Indicates	F0/F1	F2	F3	F4
	No/Mild fibrosis	Moderate fibrosis	Severe fibrosis	Cirrhosis
	Indicates no or minimal liver fibrosis and no evidence of progressive liver disease.	Indicates significant liver fibrosis and evidence of progressive liver disease.	Indicates severe liver fibrosis and high risk progression to cirrhosis.	Indicates extensive liver fibrosis consistent with cirrhosis.

Signs of advanced liver disease

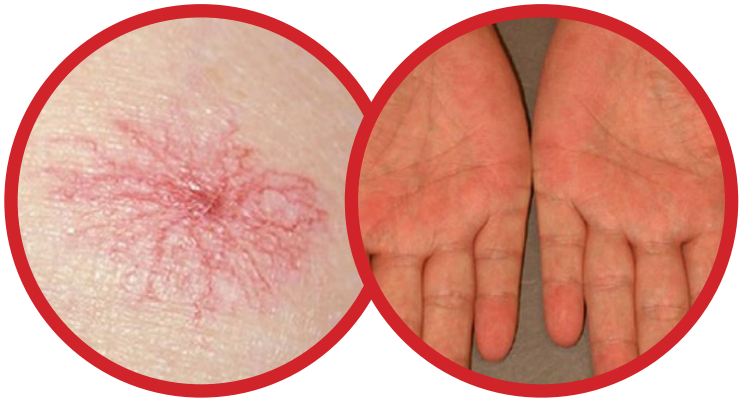
Liver disease, caused by HCV infection, can cause many signs and symptoms. As the disease evolves, signs can appear in many people – but not all, even when cirrhosis is present. Once the disease is well advanced, the features of hepatic decompensation and portal hypertension may appear, including ascites, jaundice, bleeding varices, coagulopathy, encephalopathy and renal failure.

Clinicians need to know what to look for as part of the process for staging liver disease. Cirrhosis severity can be staged by the Child-Pugh, and is based on serum bilirubin, serum albumin, INR, presence of ascites and presence of encephalopathy.

The Fib 4 (Fibrosis 4) score is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver. A Fib 4 calculator can be found at https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

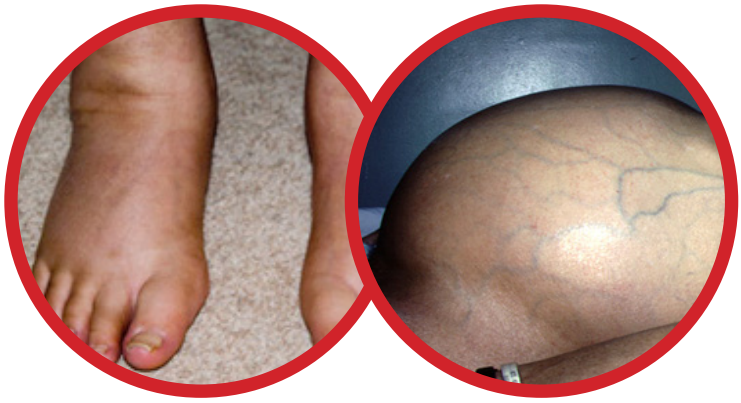
An Enhanced Liver Fibrosis (ELF) score can also be used to help estimate fibrosis. The ELF score combines quantitative serum concentration measurements of three fibrosis markers. Find out more about ELF scores at www.gpnotebook.co.uk/simplepage.cfm?ID=x2016072075237544321

Physical examination findings in chronic liver disease (of any aetiology) may include hepatomegaly and splenomegaly. A wide variety of non-specific signs (e.g. leukonychia, palmer erythema and gynaecomastia) have been associated with liver disease but these signs are of limited value. It is important to determine whether there are any signs of liver decompensation and the physical examination should focus on looking for these features. If there is doubt as to the severity of the liver disease the patient should be discussed with local experts.



Physical examination findings associated with decompensated liver disease

- Signs of hepatic encephalopathy: Drowsiness, asterixis (or 'hepatic flap')
- Jaundice
- Ascites
- Peripheral edema
- Bruising



Complications of chronic liver disease and cirrhosis

- Portal hypertension – varices on endoscopy
- Ascites – may be detected clinically or on ultrasound examination
- Hypersplenism (with or without splenomegaly)
- Synthetic dysfunction
- Hypoalbuminaemia
- Coagulopathy
- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatopulmonary and hepatorenal syndromes

Some of the most common extra-hepatic manifestations of HCV infection are described here.

Immune-mediated

Hematologic

- Mixed cryoglobulinemia (10-25% of HCV people have cryoglobulins but this is rarely symptomatic)
- Cryoglobulinaemic vasculitis
- B-cell non-Hodgkins's lymphoma
- Monoclonal gammopathy
- Immune-mediated thrombocytopenia

Rheumatologic

- Sicca syndrome
- Arthralgia/myalgia
- Autoantibody production (ie, cryoglobulin, rheumatoid factor, ANA, anticardiolipin Ab, antithyroid Abs, anti-SM Ab)
- Polyarteritis nodosa

Inflammatory-related

Renal

- Glomerulonephritis
- Nephrotic syndrome

Endocrine

- Type 2 diabetes mellitus
- Insulin resistance

Central and peripheral nervous system

- Depression
- Cognitive impairment
- Peripheral neuropathy

Systemic

- Fatigue

Dermatologic

- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotising vasculitis

Other causes of liver damage

When determining how to treat HCV, other causes of liver disease also need to be identified, as these can influence treatment options.

Identifying other causes of liver disease		
Condition	Test	Comment
Non-alcoholic fatty liver disease	Weight BMI Abdominal ultrasound	Very common
Alcoholic liver disease	History CBC LFT	Raised MCV, AST>ALT, raised triglycerides. History of alcohol consumption.
Hepatitis B infection HIV infection	Serology HBsAg anti-HBs anti-HBc HIV Ab	Vaccinate for hepatitis B if non-immune. Check for viral coinfection.
Haemochromatosis	Iron studies Genetic testing	Prevalence 1:400 but gene penetration is low and disease is much less common than the genotype implies.
Autoimmune liver disease	Auto-antibodies	Uncommon, associated with other autoimmune disease
Medication-induced liver disease	Patient history	
Alpha-1-antitrypsin	Alpha 1 antitrypsin	Rare
Wilson's disease	Family history Ceruloplasmin	Very rare Autosomal recessive Symptoms onset usually in adolescence and early 20s.

Understanding cirrhosis

Assessing liver fibrosis helps determine whether the patient could have cirrhosis. Cirrhosis is a histological diagnosis indicating liver disease with necrosis, collapse of architecture, regeneration, and fibrosis surrounding nodules of liver tissue. Cirrhotic status determines treatment regimen and length of treatment, and determines whether the patient needs specialist care.

Assessing severity

Assessing the severity of liver disease is not an exact science, but we can make an excellent attempt if we have:

- A good history to identify risk, likely duration, confounding factors, current symptoms
- A good physical examination to document any evidence of advancing liver disease
- An understanding of liver function tests and consistent use of these for diagnosis and monitoring
- An understanding of other investigations, which may provide insights into disease severity and/or the nature of the factors contributing to the presentation.

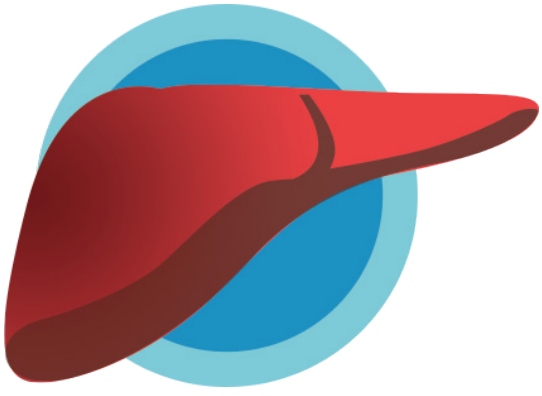
In the presence of cirrhosis and portal hypertension, hypersplenism develops and this leads to reduced haemoglobin, white cell count and platelet count (pancytopaenia). In many, the platelet count falls first and a count of < 100,000 is a surrogate marker of cirrhosis reflecting both the hypersplenism and a reduced production of thrombopoietin by the damaged liver.

Types of cirrhosis

In compensated cirrhosis, no complications have occurred.

Decompensated cirrhosis shows the presence of complications of liver dysfunction and/or portal hypertension. Symptoms include:

- Jaundice
- Hepatic encephalopathy
- Ascites and peripheral oedema
- Variceal haemorrhage



Lab markers of cirrhosis

Blood tests can help identify cirrhosis. Common markers include:

- Reduced platelet count – a count of <100 often indicates cirrhosis
- Lower albumin, total protein
- Lower platelets
- Increased globulin
- Prolonged INR or PT
- Increased bilirubin
- Liver enzymes elevation AST>ALT

Low albumin and platelets <150 are early markers of cirrhosis.

How to assess

Cirrhosis can be assessed through FibroScan® and APRI scores, described in the **HCV Testing** resource.

The Child-Pugh score is a scoring system that can also be used to measure the severity of chronic liver disease inclusive of cirrhosis. A higher score indicates worsening liver function. The score is calculated using several categories:

- total bilirubin, µmol/l (mg/dl)
- serum albumin, g/l
- INR
- presence of ascites
- presence of hepatic encephalopathy

Due to the complexity of managing cirrhosis, it is recommended that patients are managed in conjunction with your local liver unit.

Co-factors in the development of cirrhosis

- Heavy alcohol intake (>4 standard drinks per day)
- Co-infection with HIV or HBV
- Obesity
- Insulin resistance and/or metabolic syndrome
- Autoimmune liver disease – AICAH, PBC, PSC
- Metabolic disorders – haemochromatosis, Wilsons
- a-1 antitrypsin deficiency
- Primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia
- Chronic inflammatory conditions (e.g. sarcoidosis)

HCV treatment and pregnancy

Administration of PEG-IFN and/or ribavirin in pregnancy is contra-indicated. Animal studies have demonstrated that ribavirin causes birth defects and/or foetal deaths while PEG-IFN is abortifacient.

Ribavirin

Treatment with ribavirin is not recommended during pregnancy or for women who are unable or unwilling to adhere to use of adequate contraception. This includes women who are receiving ribavirin themselves; and/or women who are sexual partners of male patients who are receiving ribavirin.

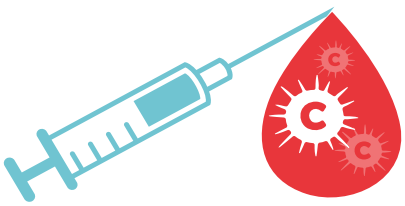
Daclatasvir

Although there is no data regarding daclatasvir for pregnant women, administration is not recommended.

In animal reproduction studies in rats and rabbits, embryo-foetal toxicity was observed in maternally toxic doses that produced exposures of 33 and 98 times the human exposure, respectively, at the recommended human dose of 60 mg.

Other treatments

Other HCV DAA drugs it is recommended that pregnancy is avoided (including sofosbuvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir, dasabuvir, grazoprevir/elbasvir, glecaprevir/pibrentasvir). They should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.



Given the lack of data, nursing mothers are advised to discontinue breastfeeding prior to commencement of HCV drug therapy.

Patients and pregnancy

Clinicians will need to advise patients who are either planning to become pregnant, or who are already pregnant, about how to manage treatment.

Planning pregnancy

Female patients who have received ribavirin, and female sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after stopping ribavirin.

Pregnant

- Treatment with PEG-IFN and/or ribavirin is contra-indicated.
- Given lack of data, HCV DAAs should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Co-morbid conditions

When deciding on the appropriate HCV treatment, other causes of chronic liver disease (or factors which may affect the progression of liver disease) should be excluded as their presence can impact treatment.

Co-morbid conditions to consider include, but are not limited to:

- HIV
- Hepatitis B virus infection
- Alcohol misuse
- Non-alcoholic steatohepatitis (related to the metabolic syndrome, obesity, diabetes mellitus)
- Hemochromatosis
- Autoimmune hepatitis
- Drug-induced liver injury
- Right ventricular failure

Factors which impact on choice and delivery of HCV treatment include:

- Mental health issues
- Drug and alcohol use (as a marker of lifestyle stability)
- Cardiac disease
- Chronic renal disease
- Advanced decompensated liver disease

Specialist referral should be sought for the following:

- Extra-hepatic manifestations of HCV
  1. Mixed cryoglobulinemia
  2. Renal disease (i.e. membrano-proliferative glomerulonephritis)
  3. HCV-associated lymphoma (i.e. diffuse large B cell lymphoma [DLBCL]).
- Transplant recipients
- Hemoglobinopathies
- Bleeding disorders

How to address co-morbid conditions in HCV treatment

HIV

- There is no apparent impact of HIV co-infection on DAA efficacy. There is, however, lower SVR with interferon-based treatment in HIV/HCV co-infection as compared with HCV mono-infection.
- Consider referral to specialist.
- Drug-drug interactions between DAAs and cART require assessment.
- This population should be prioritised for treatment for both individual and population level benefit, given increasing liver-related morbidity and mortality in those with HIV/HCV co-infection and increasing HCV incidence in HIV-positive MSM.

HBV

- Screen all patients for evidence of current, or prior, HBV infection before starting treatment with DAAs (Hep B sAg, anti-Hep B core Ab, anti-Hep B sAb +/- HBV DNA).
- If diagnosis is chronic HBV (HepB sAg positive) or "occult" HBV infection (HepB sAg negative, anti-Hep B core Ab positive, HBV DNA detected), refer to specialist.
    1. Concurrent HBV nucleoside/nucleotide analogue therapy may be indicated.
    2. Monitor patients for HBV flare-ups or reactivation during treatment and post-treatment follow-up.
- Communicate MHRA/CHM advice that Direct-acting antiviral interferon-free regimens to treat chronic hepatitis C have a risk of hepatitis B reactivation (January 2017) to patient.
- Patients with HBV co-infection should be treated with the same DAA regimens, following the same rules as HCV mono-infected patients.

Mental health

- Discuss potential impact on adherence.
- Assess for drug-drug interactions.
- Multidisciplinary care should be considered.
- Assess social and financial situation.

Drug and alcohol use

- Integrated management of substance use, in combination with HCV care, as required.
- Multidisciplinary care should be considered.
- Discuss potential impact on adherence.
- Assess for drug-drug interactions, including illicit drugs.
- Encourage patient to moderate or abstain from alcohol use.
- Assess social and financial situation.
- Discuss harm reduction strategies.
- Advise about risk of reinfection with ongoing injecting following treatment.

Cardiac disease (patients on amiodarone)

Sofosbuvir is contra-indicated in patients receiving amiodarone. Life-threatening bradyarrhythmias have been reported.

Refer to specialist

Chronic renal disease

Mild to moderate renal impairment (CrCl 30 – 80 mL/min)

- Treat according to the general recommendations.
- No dose adjustments of HCV DAAs are needed.
- Monitor carefully.

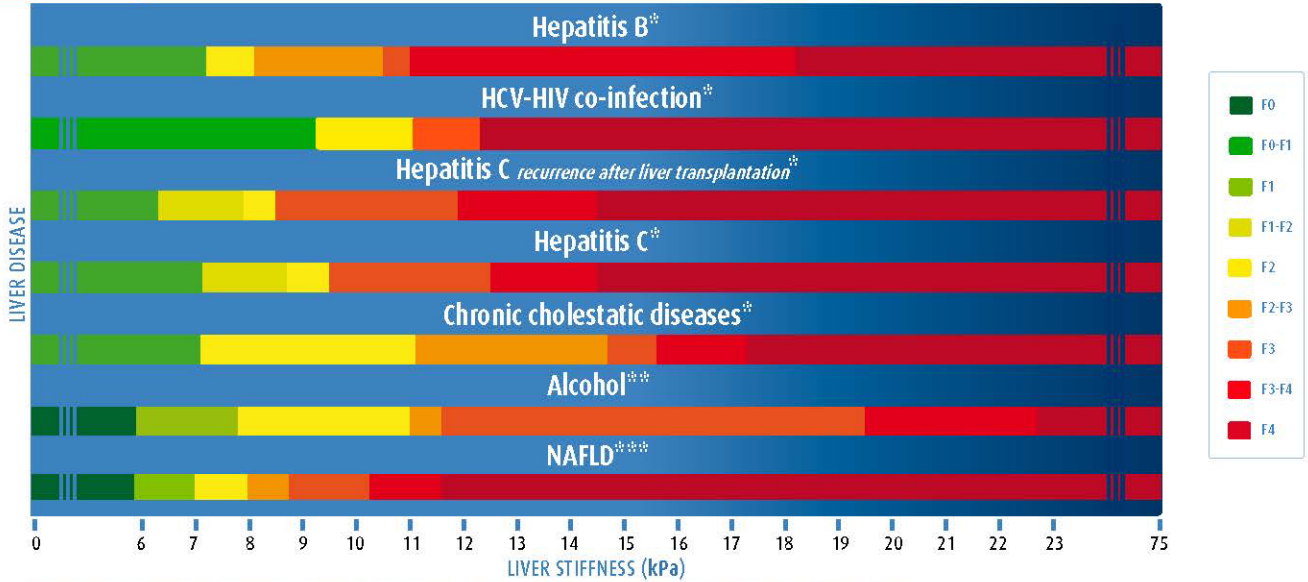
Severe renal impairment or end-stage renal disease, including hemodialysis (CrCl <30 mL/min)

Refer to specialist

- Caution with use of ribavirin given increased risk of hemolytic anemia.

SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67
**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al. , Aliment Pharmacol Ther (2008), 28, 1188-98
***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67